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(54) Title: T CELL RECEPTOR-BASED THERAPY FOR RHEUMATOID ARTHRITIS

(57) Abstract

There is provided by this invention a novel method of treating rheumatoid arthritis in a mammal. The method comprises the steps of obtaining a sample of synovium from the mammal; identifying in said sample T cell receptor variable regions; and administering to said mammal an effective amount of antibodies to at least one of said T cell receptor variable regions or antigenic fragments thereof. The invention further provides a novel method of treating rheumatoid arthritis in a mammal comprising the steps of administering to said mammal an effective amount of antibodies to mammalian T cell receptor variable regions selected from the group consisting of Vα17, Vα1, Vβ12, Vβ14, Vβ17 and Vβ7 and antigenic fragments thereof. The invention further comprises a novel method for immunizing a mammal to prevent the occurrence of rheumatoid arthritis or to treat ongoing rheumatoid arthritis. The method comprises the steps of administering to said mammal mammalian T cell receptor variable regions selected from the group consisting of Vα17, Vα1, Vβ12, Vβ14, Vβ17, Vβ7 and antigenic fragments thereof. Kits comprising mammalian T cell receptor variable regions selected from the group consisting of Vα17, Vα1, Vβ12, Vβ14, Vβ17 and Vβ7 and antigenic fragments thereof or antibodies to said variable regions are also provided by the invention.

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T CELL RECEPTOR-BASED THERAPY FOR RHEUMATOID ARTHRITIS

Cross Reference to Related Application

This application is a continuation-in-part of U.S. Serial No. 750,913 entitled "T Cell Receptor-Based Therapy for Rheumatoid Arthritis" filed in the U.S. Patent and Trademark Office on August 28, 1991 which is incorporated by reference herein.

Field of the Invention

This invention relates to the field of mammalian therapeutics. More particularly, methods of treating rheumatoid arthritis and methods for immunizing against rheumatoid arthritis are provided.

Government Rights

The work presented herein was supported in part by National Institute of Health grant 1R-29AI-28503-01. The United States Government has certain rights in the invention.

Background of the Invention

Rheumatoid arthritis (RA) is a systemic polyarthropathy characterized pathologically by proliferation of synovial fibroblast-like and macrophage-like cells and infiltration of the synovium with lymphocytes, predominately T cells of the helper (CD4+) phenotype (1,2). Such CD4+ T cells are typically activated by an antigenic peptide complexed with Class II MHC molecules (HLA-DR/DP/DQ). Immunogenetic analysis reveals that RA is associated with HLA-

DR4, and more specifically with glutamine/lysine residues at amino acids 70/71 of the HLA-DRβ chain (3-8).

Current therapy for rheumatoid arthritis is either poorly efficacious or toxic. Many lines of evidence indicate that T cells are involved in the development of rheumatoid joint disease. This includes the presence of lymphocytic infiltrates composed primarily of CD4+ T cells in the synovium (2, 21-23) the linkage of RA to HLA-DR4 which comprises a ligand for CD4+ T cell antigen receptors (3-8), and experimental models of arthritis and related autoimmune diseases which can be transferred by T cell lines (10, 13, 24-33). Studies in both animal models and human rheumatoid arthritis indicate that anti-T cell reagents can be of therapeutic efficacy (11, 25, 34-40). However, if these reagents are non-specific and delete too large a portion of the T cell repertoire, immunodeficiency (such as seen in acquired immune deficiency syndrome or AIDS) may result.

A better therapeutic alternative is to delete only those T cells involved in the autoimmune response. Since these comprise only a small portion of the total T cell repertoire, eliminating these T cells should not result in significant generalized immunosuppression.

Summary of the Invention

There is provided by this invention a novel method of treating rheumatoid arthritis in a mammal. The method comprises the steps of obtaining a sample of synovium from the mammal; identifying in said sample T cell receptor variable regions; and administering to said mammal an effective amount of antibodies to at least one of said T cell receptor variable regions or antigenic fragments thereof.

The invention further provides a novel method of treating rheumatoid arthritis in a mammal comprising the steps of administering to said mammal an effective amount of antibodies to mammalian T cell receptor variable regions selected from the group consisting of Vα17, Vα1, Vβ12, Vβ14, Vβ17 and Vβ7 and antigenic fragments thereof.

The invention further comprises a novel method for immunizing a mammal to prevent the occurrence of rheumatoid arthritis or to treat ongoing rheumatoid arthritis. The method comprises the steps of administering to said mammal mammalian T cell receptor variable regions selected from the group consisting of Vα17, Vα1, Vβ12, Vβ14, Vβ17, Vβ7 and antigenic fragments thereof.

Kits useful in the methods of the present invention comprising mammalian T cell receptor variable regions selected from the group consisting of Vα17, Vα1, Vβ12, Vβ14, Vβ17 and Vβ7 and antigenic fragments thereof or antibodies to said variable regions are also provided by the invention.

Rheumatoid arthritis (RA) is characterized by massive proliferation of synovial tissue, elevated expression of HLA DR antigens, accompanying infiltration of the tissue with CD4+ T lymphocytes, and a genetic linkage to the major histocompatility (MHC) antigen HLA-DR4. Since T cells are restricted by Class II MHC molecules such as DR4, this suggests a direct role for these CD4+ cells in pathogenesis. One strategy for the development of novel therapies in T cell mediated autoimmunity is to specifically delete the autoreactive T cells. Such a strategy depends on understanding the molecular structure of autoreactive T cell receptors (TCR). To investigate the TCR usage in RA, oligonucleotide primers specific for each of the major TCR subfamilies - one set for the TCR alpha chains and one for the TCR beta chains were used. These were utilized to amplify cDNA derived from whole synovium or synovial tissue T cell lines in a family specific manner. Amplified cDNA was sequenced to determine the corresponding amino acid sequences. Detection of amplified DNA was facilitated by utilizing oligonucleotide probes derived from the constant regions of the TCRs. Synovial T cell lines were developed by stimulation with phytohemagglutinin followed by maintenance in IL-2. The TCR repertoire present in these cell lines was quite heterogeneous, with an average of 15 alpha chains and 15.8 beta chains detected. When synovial tissue was analyzed, the

predominant TCR subfamilies detected tended to be more restricted, with an average of 4.2 alpha chains and 9.7 beta chains detected. In some synovial tissue samples predominance of one subfamily was apparent. These results suggest that while a polyclonal population of T cells is present in RA synovium, the predominant patterns of TCR transcript expression may be somewhat more restricted. This suggests that TCR based therapy of RA is possible.

Brief Description of the Drawings

Figure 1. T cell receptor specific oligonucleotides and their relative location.

Figure 2. TCR transcripts in RA synovial T cell lines. Rheumatoid synovial T cell lines were developed by initial culture in PHA for 3-5 days, then maintained in IL-2 at 10 U/ml. Following 1-3 weeks of passage, the cells were frozen, and RNA later extracted for analysis of TCR expression as outlined in Materials and Methods. The sample designations are shown on the left, with the corresponding TCR alpha and beta family-specific primers used indicated above each lane.

Figure 3. TCR transcripts in RA synovium. RNA was extracted and cDNA synthesized form 10 rheumatoid synovial tissues obtained at the time of joint surgery. These were analyzed for TCR expression as noted above. The sample designations are shown on the left, with the corresponding TCR alpha and beta family-specific primers used indicated above each lane.

Figure 4. (A) Graphic representation of the frequency of occurrence of individual alpha chain variable regions in rheumatoid synovial tissue and T cell lines;

(B) Graphic representation of the frequency of occurrence of individual beta chain variable regions in rheumatoid synovial tissue and T cell lines.

Figure 5. T cell receptor PCR primers. The asterisk denotes antisense primer. $C\beta_1$ and $C\beta_2$ primers were used mixed together in equimolar concentrations.

Figure 6. T cell receptor β chain expression in ten rheumatoid synovia. The asterisk denotes > 2 standard errors from the mean.

Figure 7. T cell receptor α chain expression in ten rheumatoid synovia. The asterisk denotes > 2 standard errors from the mean.

Detailed Description of the Invention

In one aspect of the invention a method of treating rheumatoid arthritis in a mammal, such as a human, is provided. The method comprises obtaining a sample of synovium from the mammal; identifying in said sample T cell receptor variable regions; and administering to said mammal an effective amount of antibodies to at least one of said T cell receptor variable regions or antigenic fragments thereof.

Samples of synovium such as synovial tissue or fluid are obtained as is known to those in the art.

Molecular characterization of human T cell receptors has been greatly aided recently through the application of the polymerase chain reaction (PCR). (19) *See also* e.g. U.S. patent 4,386,202 issued to Mullis which patent is incorporated by reference as if fully set forth herein. By utilizing oligonucleotide primers specific for the different T cell receptor variable region families, family specific amplification is possible (14-16). This technique can conveniently be applied to the identification of T cell receptors of interest.

Sequences of T cell receptors are generally available in the literature and in computer-based sequence data bases such as "Genbank" and "EMBL". Thus, the sequence of the family-specific oligonucleotide primer of interest can be matched against these data bases utilizing a variety of computer software tools (For example, the University of Wisconsin package. (49)) with programs such as "Word Search and Segments" or "Best Fit". The matched sequence are retrieved from the data base and translated from nucleic acid to protein sequence. Alternatively, the T cell receptors of interest can be identified by *in situ* hybridization, Northern or Southern blot analysis of synovial fluid or tissue with family-specific probes or by immunohistochemistry or immunofluorescence with antibodies to the various T cell receptor variable regions, where available.

An effective amount of antibodies to at least one of the T cell receptor variable regions is then administered

to the mammal. It should be noted that "antibodies to at least one of the T cell receptor variable regions" is meant to denote antibodies which recognize T cell receptor variable regions and portions or fragments thereof. An effective amount of antibodies is that amount which reduces the level of T cells bearing the corresponding receptor in the synovium or which results in clinical signs of improvement in the patient.

An antibody is said to be "capable of binding" a molecule if it is capable of specifically reacting with the molecule to thereby bind the molecule to the antibody. The term "epitope" is meant to refer to that portion of an antigen which can be recognized and bound by an antibody. An antigen may have one or more than one epitope. An "antigen" is a substance capable of inducing an animal to produce antibodies capable of binding to an epitope of that antigen. The specific reaction referred to above is meant to indicate that the antigen will immunoreact, in a highly selective manner, with its corresponding antibody and not with the multitude of other antibodies which may be evoked by other antigens.

The term "antibody" (Ab) or "monoclonal antibody" (Mab) as used herein is meant to include intact molecules as well as fragments thereof (such as, for example, Fab and $F(ab')_2$ fragments) which are capable of binding an antigen. Fab and $F(ab'_2)$ fragments lack the Fc fragment of intact antibody, clear more rapidly from the circulation, and may have less non-specific tissue binding.

The antibodies useful in the present invention may be prepared by any of a variety of methods. Antibodies useful in the present invention include antibodies to the T cell receptor variable region as well as antibodies to antigenic fragments thereof. Methods for the production of such antibodies are well known and described fully in the literature. (19) For example, cells expressing the peptide, synthetic peptides or an antigenic fragment thereof, can be administered to an animal in order to induce the production of sera containing polyclonal antibodies that are capable of binding the peptide. Peptides useful in the present invention

may range in size from about 25 to about 500 amino acids in length. In some embodiments of the present invention peptides may be from about 50 to about 300 amino acids in length. In still other embodiments of the present invention peptides may be from about 50 to about 200 amino acids in length. Generally, a peptide fragment is prepared and purified to render it substantially free of natural contaminants or a peptide fragment is synthesized, according to means known in the art. Either the purified fragment or the synthesized fragment or a combination of purified natural fragments and/or synthesized fragment may be introduced into an animal in order to produce polyclonal antisera of greater specific activity.

Monoclonal antibodies can be prepared using known hybridoma technology. In general, such procedures involve immunizing an animal with a peptide antigen, which includes the T cell receptor variable region and antigenic fragments thereof. The splenocytes of such animals are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention. After fusion, the resulting hybridoma cells are selectively maintained in a suitable medium and then cloned by limiting dilution. The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the peptide antigen.

If the peptide source is impure, only some of the hybridoma cells will produce antibodies capable of binding to the peptide (other hybridoma cells will produce antibody capable of binding to the peptide contaminants). Thus, it may be necessary to screen among the hybridoma cells for those which are capable of secreting an antibody which is capable of binding to the peptide. Once such a hybridoma cell has been identified, it may be clonally propagated by means known in the art in order to produce the peptide-specific monoclonal antibody.

The sequence of many human T cell receptor variable regions are known and are available in data bases such as "Gen Bank" and "EMBL". Additional sequences of interest may be

determined by cloning and sequencing cDNA clones of T cell receptors isolated from synovial tissue or fluid (48).

In particular sequences of T cell receptor variable regions Vβ14, Vβ17, Vα1 and Vα17 are preferred. Preferred DNA sequences and corresponding amino acid sequences of these regions are set forth in Table 1. Table 1 sets forth preferred sequences of rheumatoid synovial T cell receptor α and β chain variable regions derived from human synovial tissue. Such sequences and portions of said sequences are useful for the development of antibodies useful in the present invention. It should be understood by those skilled in the art that, in some embodiments of the present invention nucleic acid analogs may be substituted for naturally occuring nucleic acids. In preferred embodiments of the present invention nucleic acid sequences may range from about 75 to about 1500 nucleic acid bases in length based upon the portion of the T cell receptor variable region being coded and the size of a particular T cell receptor variable region. In other preferred embodiments nucleic acid sequences may range in length from about 150 to about 900 nucleic acid bases. In yet other embodiments of the present invention from about 150 to about 600 nucleic acids may code for a selected T cell receptor variable region or portion thereof.

Table I

I. Rheumatoid Synovial T Cell Receptor Beta Chain Nucleic Acid and Amino Acid Sequences

1. **Patient 6, Clone β14.1 (SEQ ID NO: 1)**
Family Specific Primer Vβ14

```
GTG ACT GAT AAG GGA GAT GTT CCT GAA GGG TAC AGT GTC TCT AGA GAG
Val Thr Asp Lys Gly Asp Val Pro Glu Gly Tyr Ser Val Ser Arg Glu
1               5                  10                  15

AAG AAG GAG CGC TTC TCC CTG ATT CTG GAG TCC GCC AGC ACC AAC CAG
Lys Lys Glu Arg Phe Ser Leu Ile Leu Glu Ser Ala Ser Thr Asn Gln
            20                  25                  30

ACA TCT ATG TAC CTC TGT GCC AGC AGT TCA CAA AAA CCC AAC AGT AAA
Thr Ser Met Tyr Leu Cys Ala Ser Ser Ser Gln Lys Pro Asn Ser Lys
        35                  40                  45

ACC TTC GGT TCG GGG ACC AGG TTG TCC GTT GTA GAG GAC CTG AAC AAG
Thr Phe Gly Ser Gly Thr Arg Leu Ser Val Val Glu Asp Leu Asn Lys
    50                  55                  60

GTG TTC CCA CCC GAG GTC GCT GTG TTT GAG CCA TCA GAA GCA GAG
Val Phe Pro Pro Glu Val Ala Val Phe Glu Pro Ser Glu Ala Glu
65                  70                  75
```

2. Patient 6, Clone β14.2 (SEQ ID NO:3)
Family Specific Primer Vβ14

```
GTG ACT GAT AAG GGA GAT GTT CCT GAA GGG TAC AGT GTC TCT AGA GAG
Val Thr Asp Lys Gly Asp Val Pro Glu Gly Tyr Ser Val Ser Arg Glu
1               5                  10                  15

AAG AAG GAG CGC TTC TCC CTG ATT CTG GAG TCC GCC AGC ACC AAC CAG
Lys Lys Glu Arg Phe Ser Leu Ile Leu Glu Ser Ala Ser Thr Asn Gln
            20                  25                  30

ACA TCT ATG TAC CTC TGT GCC AGC AGT TGG GGG ACT GAA GCT TTC TTT
Thr Ser Met Tyr Leu Cys Ala Ser Ser Trp Gly Thr Glu Ala Phe Phe
        35                  40                  45

GGA CAA GGC ACC AGA CTC ACA GTT GTA GAG GAC CTG AAC AAG GTG TTC
Gly Gln Gly Thr Arg Leu Thr Val Val Glu Asp Leu Asn Lys Val Phe
    50                  55                  60

CCA CCC GAG GTC GCT GTG TTT GAG CCA TCA GAA GCA GAG
Pro Pro Glu Val Ala Val Phe Glu Pro Ser Glu Ala Glu
65                  70                  75
```

3. Patient 5, Clone β14.3/4/5/6 (SEQ ID NO:5)
Family Specific Primers Vβ14

```
GAG ACT GAT AAG GGA GAT GTT CCT GAA GGG TAC AGT GTC TCT AGA GAG
Glu Thr Asp Lys Gly Asp Val Pro Glu Gly Tyr Ser Val Ser Arg Glu
1               5                  10                  15

AAG AAG GAG CGC TTC TCC CTG ATT CTG GAG TCC GCC AGC ACC AAC CAG
Lys Lys Glu Arg Phe Ser Leu Ile Leu Glu Ser Ala Ser Thr Asn Gln
            20                  25                  30

ACA TCT ATG TAC CTC TGT GCC AGC AGT TTG CTC CAG CGG ACC ACC ACA
Thr Ser Met Tyr Leu Cys Ala Ser Ser Leu Leu Gln Arg Thr Thr Thr
        35                  40                  45

GAT ACG CAG TAT TTT GGC CCA GGC ACC CGG CTG ACA GTG CTC GAG GAC
Asp Thr Gln Tyr Phe Gly Pro Gly Thr Arg Leu Thr Val Leu Glu Asp
    50                  55                  60

CTG AAA AAC GTG TTC CCA CCC GAG ATC GCT GTG TTT GAG CCA TCA GAA
Leu Lys Asn Val Phe Pro Pro Glu Ile Ala Val Phe Glu Pro Ser Glu
65                  70                  75                  80

GCA GAG
Ala Glu
```

4. Patient 5, Clone β14.7 (SEQ ID NO:7)
Family Specific Primer Vβ14

```
GTG ACT GAT AAG GGA GAT GTT CCT GAA GGG TAC AGT GTC TCT AGA GAG
Val Thr Asp Lys Gly Asp Val Pro Glu Gly Tyr Ser Val Ser Arg Glu
1               5                  10                  15

AAG AAG GAG CGC TTC TCC CTG ATT CTG GAG TCC GCC AGC ACC AAC CAG
Lys Lys Glu Arg Phe Ser Leu Ile Leu Glu Ser Ala Ser Thr Asn Gln
            20                  25                  30

ACA TCT ATG TAC CTC TGT GCC AGC AGC CTG GAC AGG GGC GAG CAG TAC
Thr Ser Met Tyr Leu Cys Ala Ser Ser Leu Asp Arg Gly Glu Gln Tyr
        35                  40                  45

TTC GGG CCG GGC ACC AGG CTC ACG GTC ACA GAG GAC CTG AAA AAC GTG
Phe Gly Pro Gly Thr Arg Leu Thr Val Thr Glu Asp Leu Lys Asn Val
    50                  55                  60

TTC CCA CCC GAG GTC GCT GTG TTT GAG CCA TCA GAA GCA GAG
Phe Pro Pro Glu Val Ala Val Phe Glu Pro Ser Glu Ala Glu
65                  70                  75
```

5. **Patient 5, Clone β14.8 (SEQ ID NO:9)**
Family Specific Primer Vβ14

```
GTG ACT GAT AAG GGA GAT GTT CCT GAA GGG TAC AGT GTC TCT AGA GAG
Val Thr Asp Lys Gly Asp Val Pro Glu Gly Tyr Ser Val Ser Arg Glu
1               5                  10                  15

AAG AAG GAG CGC TTC TCC CTG ATT CTG GAG TCC GCC AGC ACC AAC CAG
Lys Lys Glu Arg Phe Ser Leu Ile Leu Glu Ser Ala Ser Thr Asn Gln
            20                  25                  30

ACA TCT ATG TAC CTC TGT GCC AGC AGT TTA ACC TCC GTC ACA GAT ACG
Thr Ser Met Tyr Leu Cys Ala Ser Ser Leu Thr Ser Val Thr Asp Thr
        35                  40                  45

CAG TAT TTT GGC CCA GGC ACC CGG CTG ACA GTG CTC GAG GAC CTG AAA
Gln Tyr Phe Gly Pro Gly Thr Arg Leu Thr Val Leu Glu Asp Leu Lys
    50                  55                  60

AAC GTG TTC CCA CCC GAG GTC GCT GTG TTT GAG CCA TCA GAA GCA GAG
Asn Val Phe Pro Pro Glu Val Ala Val Phe Glu Pro Ser Glu Ala Glu
65                  70                  75                  80
```

6. Patient 6, Clone β17.1 (SEQ ID NO:11)
Family Specific Primer Vβ17

```
TTT CAG AAA GGA GAT ATA GCT GAA GGG TAC AGC GTC TCT CGG GAG AAG
Phe Gln Lys Gly Asp Ile Ala Glu Gly Tyr Ser Val Ser Arg Glu Lys
1               5                  10                  15

AAG GAA TCC TTT CCT CTC ACT GTG ACA TCG GCC CAA AAG AAC CCG ACA
Lys Glu Ser Phe Pro Leu Thr Val Thr Ser Ala Gln Lys Asn Pro Thr
            20                  25                  30

GCT TTC TAT CTC TGT GCC AGT AGT ATT GGG GGA CAA GGG CTA ACC GGG
Ala Phe Tyr Leu Cys Ala Ser Ser Ile Gly Gly Gln Gly Leu Thr Gly
        35                  40                  45

GCC AAA AAC ATT CAG TAC TTC GGC GCC GGG ACC CGG CCC TCA GTG CTG
Ala Lys Asn Ile Gln Tyr Phe Gly Ala Gly Thr Arg Pro Ser Val Leu
    50                  55                  60

GAG GAC CTG AAA AAC GTG TTC CCA CCC GAG GTC GCT GTG TTT GAG CCA
Glu Asp Leu Lys Asn Val Phe Pro Pro Glu Val Ala Val Phe Glu Pro
65                  70                  75                  80

TCA GAA GCA GAG
Ser Glu Ala Glu
```

7. Patient 6, Clone β17.2 (SEQ ID NO:13)
Family Specific Primer Vβ17

```
TTT CAG AAA GGA GAT ATA GCT GAA GGG TAC AAA GTC TCT CGA AAA GAG
Phe Gln Lys Gly Asp Ile Ala Glu Gly Tyr Lys Val Ser Arg Lys Glu
1               5                  10                  15

AAG AGG AAT TTC CCC CTG ATC CTG GAG TCG CCC AGC CCC AAC CAG ACC
Lys Arg Asn Phe Pro Leu Ile Leu Glu Ser Pro Ser Pro Asn Gln Thr
            20                  25                  30

TCT CTG TAC TTC TGT GCC AGC AGT TTG GGG GGA ACC TAC AAT GAG CAG
Ser Leu Tyr Phe Cys Ala Ser Ser Leu Gly Gly Thr Tyr Asn Glu Gln
        35                  40                  45

TTC TTC GGG CCA GGG ACA CGG CTC ACC GTG CTA GAG GAC CTG AAA AAC
Phe Phe Gly Pro Gly Thr Arg Leu Thr Val Leu Glu Asp Leu Lys Asn
    50                  55                  60

GTG TTC CCA CCC GAG GTC GCT GTG TTT GAG CCA TCA GAA GCA GAG
Val Phe Pro Pro Glu Val Ala Val Phe Glu Pro Ser Glu Ala Glu
65                  70                  75
```

8. Patient 6, Clone β17.3 (SEQ ID NO: 33)
Family Specific Primer Vβ17

```
TTT CAG AAA GGA GAT ATA GCT GAA GGG TAC AAA GTC TCT CGA AAA GAG
Phe Gln Lys Gly Asp Ile Ala Glu Gly Tyr Lys Val Ser Arg Lys Glu
1               5                  10                  15

AAG AGG AAT TTC CCC CTG ATC CTG GAG TCG CCC AGC CCC AAC CAG ACC
Lys Arg Asn Phe Pro Leu Ile Leu Glu Ser Pro Ser Pro Asn Gln Thr
            20                  25                  30

TCT CTG TAC TTC TGT GCC AGC AGT CCG TTC TCT CGA GCA TCC TAT GGC
Ser Leu Tyr Phe Cys Ala Ser Ser Pro Phe Ser Arg Ala Ser Tyr Gly
        35                  40                  45

TAC ACC TTC GGT TCG GGG AAC AGG TTA ACC GTT GTA GAG GAC CTG AAA
Tyr Thr Phe Gly Ser Gly Asn Arg Leu Thr Val Val Glu Asp Leu Lys
    50                  55                  60

AAC GTG TTC CCA CCC GAG GTC GCT GTG TTT GAG CCA TCA GAA GCA GAG
Asn Val Phe Pro Pro Glu Val Ala Val Phe Glu Pro Ser Glu Ala Glu
65                  70                  75                  80
```

II. Rheumatoid Synovial T Cell Receptor Alpha Chains Nucleic Acid and Amino Acid Sequences

9. Patient 1, Clone α1.1/2 (SEQ ID NO:15)
Family Specific Primer Vα1

```
CTG AGG TGC AAC TAT TCC TAT GGG GCA ACA CCT TAT CTC TTC TGG TAT
Leu Arg Cys Asn Tyr Ser Tyr Gly Ala Thr Pro Tyr Leu Phe Trp Tyr
1               5                  10                  15

GTC CAG TCC CCC GGC CAA GGC CTC CAG CTG CCC CTG AAG TAC TTT TCA
Val Gln Ser Pro Gly Gln Gly Leu Gln Leu Pro Leu Lys Tyr Phe Ser
            20                  25                  30

GGA GAC ACT CTG GTT CAA GGC ATT AAA GGC TTT GAG GCT GAA TTT AAG
Gly Asp Thr Leu Val Gln Gly Ile Lys Gly Phe Glu Ala Glu Phe Lys
        35                  40                  45

AGG AGT CAA TCT TCC TTC AAT CTG AGG AAA CCC TCT GTG CAT TGG AGT
Arg Ser Gln Ser Ser Phe Asn Leu Arg Lys Pro Ser Val His Trp Ser
    50                  55                  60

GAT GCT GCT GAG TAC TTC TGT GCT GTG GGT GCT GAT TCA GGA TAC AGC
Asp Ala Ala Glu Tyr Phe Cys Ala Val Gly Ala Asp Ser Gly Tyr Ser
65                  70                  75                  80

ACC CTC ACC TTT GGG AAG GGG ACT ATG CTT CTA GTC TCT CCA GAT ATC
Thr Leu Thr Phe Gly Lys Gly Thr Met Leu Leu Val Ser Pro Asp Ile
                85                  90                  95

CAG AAC CCT GAC CCT GCC GTG TAC CAG CTG AGA GAC TCT AAA TCC AGT
Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp Ser Lys Ser Ser
            100                 105                 110

GAC AAG
Asp Lys
```

10. Patient 2, Clone α1.3 (SEQ ID NO:17)
Family Specific Primer Vα1

```
CTG AGG TGC AAC TAT TCC TAT GGG GCA ACA CCT TAT CTC TTC TGG TAT
Leu Arg Cys Asn Tyr Ser Tyr Gly Ala Thr Pro Tyr Leu Phe Trp Tyr
1               5                  10                  15

GTC CAG TCC CCC GGC CAA GGC CTC CAG CTG CTC CTG AAG TAC TTT TCA
Val Gln Ser Pro Gly Gln Gly Leu Gln Leu Leu Leu Lys Tyr Phe Ser
            20                  25                  30

GGA GAC ACT CTG GTT CAA GGC ATT AAA GGC TTT GAG GCT GAA TTT AAG
Gly Asp Thr Leu Val Gln Gly Ile Lys Gly Phe Glu Ala Glu Phe Lys
        35                  40                  45

AGG AGT CAA TCT TCC TTC AAT CTG AGG AAA CCC TCT GTG CAT TGG AGT
Arg Ser Gln Ser Ser Phe Asn Leu Arg Lys Pro Ser Val His Trp Ser
    50                  55                  60

GAT GCT GCT GAG TAC TTC TGT GCT GTG GGT CCC ACC CAC AAT GAC ATG
Asp Ala Ala Glu Tyr Phe Cys Ala Val Gly Pro Thr His Asn Asp Met
65                  70                  75                  80

CGC TTT GGA GCA GGG ACC AGA CTG ACA GTA AAA CCA AAT ATC CAG AAC
Arg Phe Gly Ala Gly Thr Arg Leu Thr Val Lys Pro Asn Ile Gln Asn
                85                  90                  95

CCT GAC CCT GCC GTG TAC CAG CTG AGA GAC TCT AAA TCC AGT GAC AAG
Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys
            100                 105                 110
```

11. Patient 2, Clone α1.4 (SEQ ID NO: 19)
Family Specific Primer Vα1

```
CTG AGG TGC AAC TAT TCC TAT TCT GGG AGT CCT GAA CTC TTC TGG TAT
Leu Arg Cys Asn Tyr Ser Tyr Ser Gly Ser Pro Glu Leu Phe Trp Tyr
1               5                  10                  15

GTC CAG TAC TCC AGA CAA CGC CTC CAG TTA CTC TTG AGA CAC ATC TCT
Val Gln Tyr Ser Arg Gln Arg Leu Gln Leu Leu Leu Arg His Ile Ser
            20                  25                  30

AGA GAG AGC ATC AAA GGC TTC ACT GCT GAC CTT AAC AAA GGC GAG ACA
Arg Glu Ser Ile Lys Gly Phe Thr Ala Asp Leu Asn Lys Gly Glu Thr
        35                  40                  45

TCT TTC CAC CTG AAG AAA CCA TTT GCT CAA GAG GAA GAC TCA GCC ATG
Ser Phe His Leu Lys Lys Pro Phe Ala Gln Glu Glu Asp Ser Ala Met
    50                  55                  60

TAT TAC TGT GCT CTA GCG CTG CAG GCA ACA AGC TTA CTT TTG GAG GAG
Tyr Tyr Cys Ala Leu Ala Leu Gln Ala Thr Ser Leu Leu Leu Glu Glu
65                  70                  75                  80

GAA CCC AGG GTG CTA GTT AAA CCA AAT ATC CAG AAC CCT GAC CCT GCC
Glu Pro Arg Val Leu Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala
                85                  90                  95

GTG TAC CAG CTG AGA GAC TCT AAA TCC AGT GAC AAG
Val Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys
            100                 105
```

12. Patient 2, Clone α17.1 (SEQ ID NO: 25)
Family Specific Primer Vα17

```
C TTG TCA CTG GAT TTA GAG TCT CTC AGC TGC AGT TAC ACA GTC AGC
  Leu Ser Leu Asp Leu Glu Ser Leu Ser Cys Ser Tyr Thr Val Ser
    1               5                  10                  15

GGT TTA AGA GGG CTG TTC TGG TAT AGG CAA GAT CCT GGG AAA GGC CCT
Gly Leu Arg Gly Leu Phe Trp Tyr Arg Gln Asp Pro Gly Lys Gly Pro
                20                  25                  30

GAA TTC CTC TTC ACC CTG TAT TCA GCT GGG GAA GAA AAG GAG AAA GAA
Glu Phe Leu Phe Thr Leu Tyr Ser Ala Gly Glu Glu Lys Glu Lys Glu
            35                  40                  45

AGG CTA AAA GCC ACA TTA ACA AAG AAG GAA AGC TTT CTG CAC ATC ACA
Arg Leu Lys Ala Thr Leu Thr Lys Lys Glu Ser Phe Leu His Ile Thr
        50                  55                  60

GCC CCT AAA CCT GAA GAC TCA GCC ACT TAT CTC TGT GCT GTG AGG CGA
Ala Pro Lys Pro Glu Asp Ser Ala Thr Tyr Leu Cys Ala Val Arg Arg
    65                  70                  75

TCA GAT GGC CAG AAG CTG CTC TTT GCA AGG GGA ACC ATG TTA AAG GTG
Ser Asp Gly Gln Lys Leu Leu Phe Ala Arg Gly Thr Met Leu Lys Val
80                  85                  90                  95

GAT CTT AAT ATC CAG AAC CCT GAC CCT GCC GTG TAC CAG CTG AGA GAC
Asp Leu Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp
                100                 105                 110

TCT AAA TCC AGT GAC AAG
Ser Lys Ser Ser Asp Lys
            115
```

13. **Patient 3, Clone α17.2 (SEQ ID NO:23)**
Family Specific Primer Vα17

```
C TTG TCA CTG GAT TTA GAG TCT CTC AGC TGC AGT TAC ACA GTC AGC
  Leu Ser Leu Asp Leu Glu Ser Leu Ser Cys Ser Tyr Thr Val Ser
    1               5                  10                  15

GGT TTA AGA GGG CTG TTC TGG TAT AGG CAA GAT CCT GGG AAA GGC CCT
Gly Leu Arg Gly Leu Phe Trp Tyr Arg Gln Asp Pro Gly Lys Gly Pro
                20                  25                  30

GAA TTC CTC TTC ACC CTG TAT TCA GCT GGG GAA GAA AAG GAG AAA GAA
Glu Phe Leu Phe Thr Leu Tyr Ser Ala Gly Glu Glu Lys Glu Lys Glu
            35                  40                  45

AGG CTA AAA GCC ACA TTA ACA AAG AAG GAA AGC TTT CTG CAC ATC ACA
Arg Leu Lys Ala Thr Leu Thr Lys Lys Glu Ser Phe Leu His Ile Thr
        50                  55                  60

GCC CCT AAA CCT GAA GAC TCA GCC ACT TAT CTC TGT GCT GTG AGG CGA
Ala Pro Lys Pro Glu Asp Ser Ala Thr Tyr Leu Cys Ala Val Arg Arg
    65                  70                  75

TCA GAT GGC CAG AAG CTG CTC TTT GCA AGG GGA ACC ATG TTA AAG GTG
Ser Asp Gly Gln Lys Leu Leu Phe Ala Arg Gly Thr Met Leu Lys Val
80                  85                  90                  95

GAT CTT AAT ATC CAG AAC CCT GAC CCT GCC GTG TAC CAG CTG AGA GAC
Asp Leu Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp
                100                 105                 110

TCT AAA TCC AGT GAC AAG
Ser Lys Ser Ser Asp Lys
            115
```

14. Patient 4, Clone α17.3 (SEQ ID NO: 21)
Family Specific Primer Vα17

```
C TTG TCA CTG GAT TTA GAG TCT CTC AGC TGC AGT TAC ACA GTC AGC
  Leu Ser Leu Asp Leu Glu Ser Leu Ser Cys Ser Tyr Thr Val Ser
  1               5                  10                  15

GGT TTA AGA GGG CTG TTC TGG TAT AGG CAA GAT CCT GGG AAA GGC CCT
Gly Leu Arg Gly Leu Phe Trp Tyr Arg Gln Asp Pro Gly Lys Gly Pro
                20                  25                  30

GAA TTC CTC TTC ACC CTG TAT TCA GCT GGG GAA GAA AAG GAG AAA GAA
Glu Phe Leu Phe Thr Leu Tyr Ser Ala Gly Glu Glu Lys Glu Lys Glu
            35                  40                  45

AGG CTA AAA GCC ACA TTA ACA AAG AAG GAA AGC TTT CTG CAC ATC ACA
Arg Leu Lys Ala Thr Leu Thr Lys Lys Glu Ser Phe Leu His Ile Thr
        50                  55                  60

GCC CCT AAA CCT GAA GAC TCA GCC ACT TAT CTC TGT GCT GCG AGG CGA
Ala Pro Lys Pro Glu Asp Ser Ala Thr Tyr Leu Cys Ala Ala Arg Arg
    65                  70                  75

TCA GAT GGC CAG AAG CTG CTC TTT GCA AGG GGA ACC ATG TTA AAG GTG
Ser Asp Gly Gln Lys Leu Leu Phe Ala Arg Gly Thr Met Leu Lys Val
80                  85                  90                  95

GAT CTT AAT ATC CAG AAC CCT GAC CCT GCC GTG TAC CAG CTG AGA GAC
Asp Leu Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp
                100                 105                 110

TCT AAA TCC AGT GAC AAG
Ser Lys Ser Ser Asp Lys
            115
```

15. Patient 4, Clone α17.4 (SEQ ID NO: 27)
Family Specific Primer Vα17

```
C TTG TCA CTG GAT TTA GAG TCT CTC AGC TGC AGT TAC ACA GTC AGC
  Leu Ser Leu Asp Leu Glu Ser Leu Ser Cys Ser Tyr Thr Val Ser
    1               5                  10                  15

GGT TTA AGA TGG CTG TTC TGG TAT AGG CAA GAT CCT GGG AAA GGC CCT
Gly Leu Arg Trp Leu Phe Trp Tyr Arg Gln Asp Pro Gly Lys Gly Pro
                  20                  25                  30

GAA TTC CTC TTC GCC CTG TAT TCA GCT GGG GAA GAA AAG GAG AAA GAA
Glu Phe Leu Phe Ala Leu Tyr Ser Ala Gly Glu Glu Lys Glu Lys Glu
             35                  40                  45

AGG CTA AAA GCC ACA TTA ACA AAG AAG GAA AGC TTT CTG CAC ATC ACA
Arg Leu Lys Ala Thr Leu Thr Lys Lys Glu Ser Phe Leu His Ile Thr
         50                  55                  60

GCC CCT AAA CCT GAA GAC TCA GCC ACT TAT CTC TGT GCT GTG AGG CGA
Ala Pro Lys Pro Glu Asp Ser Ala Thr Tyr Leu Cys Ala Val Arg Arg
     65                  70                  75

TCA GAT GGC CAG AAG CTG CTC TTT GCA AGG GGA ACC ATG TTA AAG GTG
Ser Asp Gly Gln Lys Leu Leu Phe Ala Arg Gly Thr Met Leu Lys Val
 80                  85                  90                  95

GAT CTT AAT ATC CAG AAC CCT GAC CCT GCC GTG TAC CAG CTG AGA GAC
Asp Leu Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp
                 100                 105                 110

TCT AAA TCC AGT GAC AAG
Ser Lys Ser Ser Asp Lys
            115
```

16. Patient 7, Clone α17.5 (SEQ ID NO: 29)
Family Specific Primer Vα17

```
A GAT GTC TCC ATG AAC TGC ACT TCT TCA AGC ATA TTT AAC ACC TGG
  Asp Val Ser Met Asn Cys Thr Ser Ser Ser Ile Phe Asn Thr Trp
    1               5                  10                  15

CTA TGG TAC AAG CAG GAC CCT GGG GAA GGT CCT GTC CTC TTG ATA GCC
Leu Trp Tyr Lys Gln Asp Pro Gly Glu Gly Pro Val Leu Leu Ile Ala
                  20                  25                  30

TTA TAT AAG GCT GGT GAA TTG ACC TCA AAT GGA AGA CTG ACT GCT CAG
Leu Tyr Lys Ala Gly Glu Leu Thr Ser Asn Gly Arg Leu Thr Ala Gln
             35                  40                  45

TTT GGT ATA ACC AGA AAG GAC AGC TTC CTG AAT ATC TCA GCA TCC ATA
Phe Gly Ile Thr Arg Lys Asp Ser Phe Leu Asn Ile Ser Ala Ser Ile
         50                  55                  60

CCT AGT GAT GTA GGC ATC TAC TTC TGT GCT GGG CAG GCC CTC ACC GGT
Pro Ser Asp Val Gly Ile Tyr Phe Cys Ala Gly Gln Ala Leu Thr Gly
     65                  70                  75

AAC CAG TTC TAT TTT GGG ACA GGG ACA AGT TTG ACG GTC ATT CCA AAT
Asn Gln Phe Tyr Phe Gly Thr Gly Thr Ser Leu Thr Val Ile Pro Asn
 80                  85                  90                  95

ATC CAG AAC CCT GAC CCT GCC GTG TAC CAG CTG AGA GAC TCT AAA TCC
Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp Ser Lys Ser
                100                 105                 110

AGT GAC AAG
Ser Asp Lys
```

17. Patient 4, Clone α17.6 (SEQ ID NO:31)
Family Specific Primer Vα17

```
CTT GTC ACT GGA TTT AGA GTC TCT CAG CTG GTG GAG CAG AGC CCT CAA
Leu Val Thr Gly Phe Arg Val Ser Gln Leu Val Glu Gln Ser Pro Gln
1               5                  10                  15

TCT TTG ATA GTC CAG AAA GGA GGG ATT TCA ATT ATA AAC TGT GCT TAT
Ser Leu Ile Val Gln Lys Gly Gly Ile Ser Ile Ile Asn Cys Ala Tyr
            20                  25                  30

GAG AAC ACT GCG TTT GAC TAC TTT CCA TGG TAC CAA CAA TTC CCT GGG
Glu Asn Thr Ala Phe Asp Tyr Phe Pro Trp Tyr Gln Gln Phe Pro Gly
        35                  40                  45

AAA GGC CCT GCA TTA TTG ATA GCC ATA CGT CCA GAT GTG AGT GAA AAG
Lys Gly Pro Ala Leu Leu Ile Ala Ile Arg Pro Asp Val Ser Glu Lys
    50                  55                  60

AAA GAA GGA AGA TTC ACA ATC TCC TTC AAT AAA AGT GCC AAG CAG TTC
Lys Glu Gly Arg Phe Thr Ile Ser Phe Asn Lys Ser Ala Lys Gln Phe
65                  70                  75                  80

TCA TTG CAT ATC ATG GAT TCC CAG CCT GGA GAC TCA GCC ACC TAC TTC
Ser Leu His Ile Met Asp Ser Gln Pro Gly Asp Ser Ala Thr Tyr Phe
                85                  90                  95

TGT GCA GCA GAG GGA GGA AAG CTT ATC TTC GGA CAG GGA ACG GAG TTA
Cys Ala Ala Glu Gly Gly Lys Leu Ile Phe Gly Gln Gly Thr Glu Leu
            100                 105                 110
```

```
TCT GTG AAA CCC AAT ATC CAG AAC CCT GAC CCT GCC GTG TAC CAG CTG
Ser Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu
        115             120             125

AGA GAC TCT AAA TCC AGT GAC AAG
Arg Asp Ser Lys Ser Ser Asp Lys
    130             135
```

Antibodies may be developed against the T cell receptors or against amino acid sequences and portions thereof, corresponding to said T cell receptor variable regions such as those set forth in Table 1 for commercial purposes by developing monoclonal antibodies as indicated herein and known in the art. These murine or rat or other species monoclonals could be administered directly. Alternatively, to reduce xenogeneic responses to the monoclonals, these antibodies can be "humanized" by grafting a human constant region onto the non-human variable region, or by transplanting the non-human hypervariable regions onto a human antibody. (50, 51) Polyclonal antibodies can also be employed, particularly if they are from a species which exhibits little immunogenicity in humans such as pigs. Antigenic fragments may be derived from family-specific sequences such as those contained in the variable region primers or from hypervariable regions as defined in Jones et al. (52)

The association of RA with HLA-is reminiscent of similar associations seen in experimental models of autoimmunity, such as experimental autoimmune encephalomyelitis, a model for multiple sclerosis triggered by autoreactive T cells reactive to myelin basic protein and specific MHC Class II antigens (9-12). The observation of a restriction to certain MHCs in such experimental systems correlates with a restricted repertoire of T cell antigen receptors which respond to that MHC + antigen (13). This has also been documented in multiple sclerosis T cell lines derived from humans (14, 15). In experimental systems, antibodies directed to the relevant T cell receptors, or immunization with peptides derived from these T cell receptors, is capable of ameliorating the disease (10, 11).

In another embodiment of the invention a method of treating rheumatoid arthritis in a mammal is provided which comprises administering to said mammal an effective amount of antibodies to mammalian T cell receptor variable regions selected from the group consisting of Vα17, Vα1, Vβ12, Vβ14,

Vβ17 and Vβ7 and antigenic fragments thereof. In particular, antibodies to amino acid set forth in Table 1 and portions thereof are preferred.

Antibodies to mammalian T cell receptor variable regions selected from the group consisting of Vα17, Vα1, Vβ12, Vβ14, Vβ17 and Vβ7 and antigenic fragments thereof can be prepared as described above.

An effective amount of antibodies to at least one of the T cell receptor variable regions described above is then administered to the mammal. An effective amount of antibodies is that amount which reduces the level of T cells bearing the corresponding receptor in the synovium or which results in clinical signs of improvement in the patient.

Of course the method of treating rheumatoid arthritis of the present invention may be combined with other traditional treatments for the disease where indicated.

It is believed the therapy of the invention could be administered at any point in the course of rheumatoid arthritis.

A method for immunizing a mammal to prevent the occurrence of rheumatoid arthritis or to ameliorate active disease is also provided by the invention. The method comprises administering to said mammal mammalian T cell receptor variable regions selected from the group consisting of Vα17, Vα1, Vβ12, Vβ17, Vβ7 and antigenic fragments thereof. Amino acid sequences as set forth in Table 1, and portions thereof, are preferred for some embodiments of the invention.

Mammals could be immunized by using the T cell receptor variable regions described above and antigenic fragments thereof, with or without agents known to those in the art attached thereto to increase the antigenic potential of the antigen. Generally the antigen or protein can be dissolved at between about 1μg/ml to about 1g/ml in sterile saline or saline with 0.4 mg aluminum hydroxide per ml as a vehicle. Generally 0.5 to 1.0 ml of the protein solution is injected intramuscularly and then followed by booster injections at one and 6-12 months after the initial

immunization. An effective amount is that amount of antigen sufficient to raise antibodies to the antigen in the animal.

There is precedence for immunizing mammals with T cell receptor variable regions as protection against experimental autoimmune encephalomyelitis. (11, 12) It is believed that a patient to be immunized would either have clinical evidence of rheumatoid arthritis, have a strong family history of rheumatoid arthritis or have the genetic predisposition for rheumatoid arthritis described herein.

Kits with the antibodies described herein useful in the treatment of rheumatoid arthritis or kits with antigens for immunization are also within the scope of this invention.

Materials and Methods

Synovial tissue and Cell Lines: Tissue was obtained at the time of joint surgery, and was handled sterily at all times. The tissue was rinsed in sterile phosphate buffered saline (PBS), placed in a petri dish, the superficial layer snipped off with scissors and minced with a sterile scalpel. The minced tissue was placed in 20 mls PBS with 5% HEPES buffer, 0.4 g hyaluronidase (type 1-S), 0.04 g DNA-ase 1 (type II from bovine pancrease) and 1.2 g collagenase (Type Z) (all from Sigma, St. Louis, MO) with 1% fetal calf serum (FCS), and stirred continuously for 90 minutes at 37°C. The large chunks of tissue were decanted, and the cells centrifuged and washed twice in culture media (RPMI 1640 with pen/step, L-glutamine, sodium pyruvate, non-essential amino acids, HEPES buffer $5X10^{-5}$ M β-mercaptoethanol (all from Gibco, Gaithersburg MD), and 10% FCS (Hyclone). The T cells were purified by standard nylon wool chromatography (17), cultured overnight at $1x10^6$/ml in culture media, and the non-adherent cells separated, centrifuged, and maintained in culture. Stimulation of the cells was with either phytohemagglutinin (1% solution, from Sigma), interleukin-2 (Amgen Biologicals, Thousand Oaks, CA), or media alone. Cells were stimulated for 3-5 days, and then maintained for varying periods of time in 10 U/ml IL-2 prior to analysis.

Fluorescence-Activated Cell Sorter (FACS) Analysis: Following culture, cells were centrifuged, washed and resuspended in FACS media (1% bovine serum albumin in PBS with 0.1% sodium azide), at $1x10^6$ cells per 100μl. Primary antibody was added for 20-40 minutes on ice. After an additional two washings, the cells were subjected to second antibody (fluorescein isothiocyanate-conjugated goat anti-mouse Ig (Sigma); at 1:100 dilution), then washed twice again. The cells were then analyzed at the University of Pennsylvania Cancer Center FACS facility. Per cent positive was determined by comparing the samples to a no primary antibody control. Antibodies used were OKT3 anti-CD3 (Ortho Diagnostics,

Raritan, NJ), Leu3a anti-CD4 (Becton-Dickinson **provid location**), and OKT8 (Ortho), at the dilutions suggested by the suppliers.

RNA Extraction and cDNA Synthesis: Tissue was homogenized in guanidinum isothiocyanate (GITC) solution, or cells resuspended in GITC solution, and vortexed for 30 seconds. 0.1 ml 2 M sodium acetate pH 4 was added, the solution vortexed, followed by 1.0 ml diethylpyrocarbonate (DEP)-water-saturated phenol, the sample mixed, then 0.2 ml phenylisoamyl alcohol, thorough vortexing, and the solution transferred to sterile EPPENDORF tubes. Each sample was then incubated on ice for 20 minutes, microfuged for 10 minutes, and the top layer recovered, RNA precipitated with 2.5 volumes of 100% ethanol and 1/10 volume 1M sodium acetate pH 5.5 in dry ice/ethanol for 30 minutes. The solutions were microfuged for 15 minutes, the supernatant decanted, the pellets washed in 70% ethanol and rotary evaporated. The dried pellets were resuspended in 50 μl DEP-water and RNA quantitated spectrophotometrically.

For reverse transcription, 1-20 μg of RNA in 10μl was utilized to synthesize cDNA primed with random hexamers in the following reaction mixture: 3μl Maloney Murine Leukemia Virus reverse transcriptase with 6 μl 5x reverse transcriptase buffer, 1.5 μl RNAse inhibitor, and 3 μl 0.1 M dithiothreitol (all from GIBCO/BRL, Gaithersburg, MD), 3 μl random hexamers (from Pharmacia LKB Biotechnology, Piscataway, NJ), and either 1 or 3 μl 100 mM dNTPs (25 mM in each dNTP, from Boehringer Mannheim, GmbH W. Germany). Following a 10 minute preincubation at 25°C, the reaction was carried out for 1 hour at 42°C, then 95°C for 5 minutes followed by storage at -20°C until use.

PCR Amplification T Cell Receptor Variable Regions: cDNA was amplified utilizing the primers listed in Figure 5 with Va/βn and Ca/β_{mid} at 0.2 nM concentrations. cDNA was amplified utilizing *Thermus aquaticus* DNA polymerase (*Taq* polymerase) and standard reaction conditions suggested by the manufacturer

(Perkin-Elmer Cetus Corp., Norwalk, CT). The reaction mixture contained 10 μl of 10X reaction buffer, 16 μl 1.25 nM dNTPs (final concentration 200 μM in each dNTP), 5 μl of each oligonucleotide primer at 20 μM (final 1 μM in each primer), 5 μl of DNA, 0.5 μl of DNA, 0.5 μl *Taq* polymerase, and 58.5 ml distilled/deionized water. Primers were synthesized by the Wistar Institute oligonucleotide synthesis facility. The program utilized 5 initial low temperature cycles for low stringency (95°C for 1 min., 37°C for 2 min., 52°C for 2 min.), followed by higher stringency for 40 cycles (95°C for 1 min., 52°C for 2 min., 72°C for 2 min), and a final 5 minute 72°C elongation phase. For some experiments, the initial 20 cycles, described above, was used followed by additional increments of 5 higher stringency cycles (95°C for 1 min., 52°C for 2 min., 72°C for 2 min), with PCR product removed following each increment of 5 cycles for analysis. Products were analyzed by electrophoresis on 2-3% agarose gels stained with ethidium bromide.

Determination of Sequences of T Cell Receptor Variable Regions: PCR products were cloned into the TA cloning vector (InVitrogen, San Diego, CA) according to kit instructions. Plasmid DNA was isolated from the clones as described by Ausubel, et al., *Current Protocols in Molecular Biology* (John Wiley & Sons, New York, NY) and Sambrook, et al., *Molecular Cloning. A Laboratory Manual* (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.) incorporated by reference in their entireties. A portion of the cloned cDNA was sequenced in accordance with methods provided by Ausubel, et al., *Current Protocols in Molecular Biology* (John Wiley & Sons, New York, NY) and Sambrook, et al., *Molecular Cloning. A Laboratory Manual* (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.) incorporated by reference in their entireti s. Amino acid sequences were determined as set forth in Table 1. Relative positions set forth in Table 2 were determined in relation to family specific variable region primers used and published data providing invariant residues

TABLE II

RHEUMATOID SYNOVIAL T CELL RECEPTOR ALPHA CHAINS

CONSERVED RESIDUES	E	CN	.	WYRQ
		T	.	LVK
		S	.	HKH
		A	.	L
		D	.	Q

POSITION (Includes Leader Peptide)

1 10 20 30 40 50 60 70

Patient 1 Clone α1.1/2 (SEQ ID NO: 15)	LRCNYSYGAT.PYLFWYVQSPGQGLQLPLKYFSGDTLVQGI
Patient 2 Clone α1.3 (SEQ ID NO:17)	LRCNYSYGAT.PYLFWYVQSPGQGLQLLLKYFSGDTLVQGI
Patient 2 Clone α1.4 (SEQ ID NO:19)	LRCNYSYSGS.PELFWYVQYSRQRLQLLLRHISRES.IKG
Patient 2 Clone α17.1 (SEQ ID NO:25)	LSLDLESLSCSYTVSGLRGL.FWYRQDPGKGP.EFLFTLYSAGEEKEK
Patient 3 Clone α17.2 (SEQ ID NO:23)	LSLDLESLSCSYTVSGLRGL.FWYRQDPGKGP.EFLFTLYSAGEEKEK
Patient 4 Clone α17.3 (SEQ ID NO:21)	LSLDLESLSCSYTVSGLRGL.FWYRQDPGKGP.EFLFTLYSAGEEKEK
Patient 4 Clone α17.4 (SEQ ID NO:27)	LSLDLESLSCSYTVSGLRWL.FWYRQDPGKGP.EFLFALYSAGKEKEK
Patient 7 Clone α17.5 (SEQ ID NO:29)	DVSMNCTSSSIFNTWL..WYKQDPGEGPVLLIALYKAGELTSNG
Patient 4 Clone α17.6 (SEQ ID NO:31)	LVTGFRVSQLVEQSPQSLIVQKGGISIINCAYENTAFDYPP WYQQFPGKGPA LLIAIRPDVSEKKE

RHEUMATOID SYNOVIAL T CELL RECEPTOR BETA CHAINS

```
CONSERVED RESIDUES               V Q P   I   G     C      FWYQQ      L
                                 I   S   V   T            Y  RK      P
                                                          S  K       G

POSITION (Includes Leader Peptide)
            1        10      20       30       40      50       60       70
            |         |       |        |        |       |        |        |

Patient 6 Clone β14.1 (SEQ ID NO:1)                                            VT.DKG
Patient 6 Clone β14.2 (SEQ ID NO:3)                                            VT.DKG
Patient 5 Clone β14.3/4/5/6 (SEQ ID NO:5)                                      ET.DKG
Patient 5 Clone β14.7 (SE ID NO:7)                                             VT.DKG
Patient 5 Clone β14.8 (SEQ ID NO:9)                                            VT.DKG
Patient 6 Clone β17.1 (SEQ ID NO:11)                                           FQ. KG
Patient 6 Clone β17.2 (SEQ ID NO:13)                                           FQ..KG
Patient 6 Clone β17.3 (SEQ ID NO:33)                                           FQ. KG
```

TABLE II

RHEUMATOID SYNOVIAL T CELL RECEPTOR ALPHA CHAINS

```
CONSERVED                                         F         DS  YFCA          FG
RESIDUES                                          I          T   Y G           A
                                                  L          A   L V
                                                  V                I
                                                  S

POSITION (Includes Leader Peptide)
                                          80        90        100       110       120
                                          |         |         |         |         |
Patient 1 Clone α1.1/2 (SEQ ID NO: 15)  KGFEAEFKRSQSSFNLRKPSVHWSDAAEYFCAV...GADSGYSTLTFGKG
Patient 2 Clone α1.3 (SEQ ID NO:17)     KGFEAEFKRSQSSFNLRKPSVHWSDAAEYFCAV...GP..THNDMRFGAG
Patient 2 Clone α1.4 (SEQ ID NO:19)     FTADLNKGETS...FHLKKPFAQEEDSAMYYCAL...ALQATSLLLEEEP

Patient 2 Clone α17.1 (SEQ ID NO:25)    ERLKATLTKKESFLHITAPKPE..DSATYLCAVRRSDGQKLLFARGTMLK
Patient 3 Clone α17.2 (SEQ ID NO:23)    ERLKATLTKKESFLHITAPKPE..DSATYLCAVRRSDGQKLLFARGTMLK
Patient 4 Clone α17.3 (SEQ ID NO:21)    ERLKATLTKKESFLHITAPKPE..DSATYLCAARRSDGQKLLFARGTMLK
Patient 4 Clone α17.4 (SEQ ID NO:27)    ERLKATLTKKESFLHITAPKPE..DSATYLCAVRRSDGQKLLFARGTMLK
Patient 7 Clone α17.5 (SEQ ID NO:29)    RLTAQFGITRKDSFLNISASIP.SDVGIYFCAGQALTGNQFYFGTGTSLT
Patient 4 Clone α17.6 (SEQ ID NO:31)    GRFTISFNKSAKQFSLHIMDSQPGDSATYFCAAEGGKLI...FGQGTELS
```

RHEUMATOID SYNOVIAL T CELL RECEPTOR BETA CHAINS

CONSERVED RESIDUES	L DSS YLCAS
	M QT F SA
	H G O T
	V
POSITION (Includes Leader Peptide)	80 90 100 110
Patient 6 Clone β14.1 (SEQ ID NO:1)	DVPEGYSVSREKKERFSLILESASTNQTSMYLCASSSQKP
Patient 6 Clone β14.2 (SEQ ID NO:3)	DVPEGYSVSREKKERFSLILESASTNQTSMYLCASSWGT.
Patient 5 Clone β14.3/4/5/6 (SEQ ID NO: 5)	DVPEGYSVSREKKERFSLILESASTNQTSMYLCASSLLQR
Patient 5 Clone β14.7 (SE ID NO:7)	DVPEGYSVSREKKERFSLILESASTNQTSMYLCASSLDRG
Patient 5 Clone β14.8 (SEQ ID NO:9)	DVPEGYSVSREKKERFSLILESASTNQTSMYLCASSLTSV
Patient 6 Clone β17.1 (SEQ ID NO:11)	DIAEGYSVSREKKESFPLTVTSAQKNPTAFYLCASSIGGQ
Patient 6 Clone β17.2 (SEQ ID NO:13)	DIAEGYKVSRKEKRNFPLILESPSPNQTSLYFCASSLGGT
Patient 6 Clone β17.3 (SEQ ID NO:33)	DIAEGYKVSRKEKRNFPLILESPSPNQTSLYFCASSPFSR

TABLE II

RHEUMATOID SYNOVIAL T CELL RECEPTOR ALPHA CHAINS

CONSERVED RESIDUES	NIQ D Y
POSITION (Includes Leader Peptide)	130 140 150 | | |
Patient 1 Clone α1.1/2 (SEQ ID NO: 15)	TMLLVSPDIQNPDPAVYQLRDSKSSDK
Patient 2 Clone α1.3 (SEQ ID NO:17)	TRLTVKPNIQNPDPAVYQLRDSKSSDK
Patient 2 Clone α1.4 (SEQ ID NO:19)	.RVLVKPNIQNPDPAVYQLRDSKSSDK
Patient 2 Clone α17.1 (SEQ ID NO:25)	VDL....NIQNPDPAVYQLRDSKSSDK
Patient 3 Clone α17.2 (SEQ ID NO:23)	VDL....NIQNPDPAVYQLRDSKSSDK
Patient 4 Clone α17.3 (SEQ ID NO:21)	VDL....NIQNPDPAVYQLRDSKSSDK
Patient 4 Clone α17.4 (SEQ ID NO:27)	VDL....NIQNPDPAVYQLRDSKSSDK
Patient 7 Clone α17.5 (SEQ ID NO:29)	VIP....NIQNPDPAVYQLRDSKSSDK
Patient 4 Clone α17.6 (SEQ ID NO:31)	VKP....NIQNPDPAVYQLRDSKSSDK

RHEUMATOID SYNOVIAL T CELL RECEPTOR BETA CHAINS

CONSERVED RESIDUES FG
P

POSITION (Includes Leader Peptide)

	120 130 140 150 160
Patient 6 Clone β14.1 (SEQ ID NO:1)	NSKT...FGS...GTRFSVVEDLNKVFPPEVAVFEPSEAE
Patient 6 Clone β14.2 (SEQ ID NO:3)	.EAF...FGQ...GTRLTVVEDLNKVFPPEVAVFEPSEAE
Patient 5 Clone β14.3/4/5/6 (SEQ ID NO: 5)	TTTDTQYFGP...GTRLTVLEDLKNVFPPEIAVFEPSEAE
Patient 5 Clone β14.7 (SE ID NO:7)	EQY FGP GTRLTVTEDLKNVFPPEVAVFEPSEAE
Patient 5 Clone β14.8 (SEQ ID NO:9)	..TDTQYFGP...GTRLTVLEDLKNVFPPEVAVFEPSEAE
Patient 6 Clone β17.1 (SEQ ID NO:11)	GLTGAKNIQYFGAGTRPSVLEDLKNVFPPEVAVFEPSEAE
Patient 6 Clone β17.2 (SEQ ID NO:13)	YNEQFFGP.....GTRLTVLEDLKNVFPPEVAVFEPSEAE
Patient 6 Clone β17.3 (SEQ ID NO:33)	ASYGYT FGS GTRLTVVEDLKNVFPPEVAVFEPSEAE

and numbering of sequences of known T cell receptor regions. Kabat, E.A., et al., *Sequences of Proteins of Immunological Interest"* 4th ed., U.S. Department of Health and Human Services, Public Health Service National Institute (1987) .

Transfer and Probing Agarose gels were transferred to nylon fibers(Genescreen Plus, Du Pont New England Nuclear, Boston, MA) by capillary transfer overnight. Hybridization was with either Cα5′ or Cβ5′ primers noted in Figure 5. Oligonucleotide labeling employed 100 ng DNA, 75 μC_i ^{32}P-ATP, 2.5 μl 10 x kinase buffer (500 mM Tris HCL pH 7.6, 100 mM $MgCL_2$, 50 mM dithiothreitol, 1 mM spermadine, 1 mM EDTA), 10 U T4 DNA kinase adjusted to a final volume of 25 μl with distilled water. Labelling was carried out by incubation at 37°C for 30 minutes prior to use. Blots were prehybridized in 5x SSC, 5x Denhardt's solution, 0.1% SDS for 1-1.5 hours at 55°C in sealable polyethylene bags, most of the solution poured off, ^{32}P-labelled oligonucleotide added (75μCi) and hybridized for 2-3 hours at 42°C or overnight at 4°C, the blots washed 1x in 2x SSC, 0.1% SDS for 20 minutes at 45°C, then 3x in 5x SSC, 0.1% SDS for 20 minutes at 45°C, an exposed to Kodak XRP film at -70°C for 2-72 hours.

Statistics

The standard error of occurrence of each TCR V region family was calculated by the formulae:

$$100 \text{ times the square root of } (p[1-p]/n)$$

where "n" is the number of samples analyzed, and "p" is the number of positives. The frequency of occurrence of a particular TCR V region family was considered significantly increased if it was ≥ 2 standard errors higher than the mean for all V regions of that type (α versus β).

Results

PCR Prim rs

Primers derived from the human TCR alpha and beta constant regions were utilized in conjunction with primers specific for individual variable region families. (14-16). The primers utilized in these studies are listed in Fig. 5, and their relative positions on the coding strand of cDNA indicated in Figure 1. The constant region primers were designed as antisense primers to allow their use to prime both PCR reactions as well as probes for blotting. Variable region primers were designed to act in a family specific manner as has been previously reported (14-16).

The PCR program used in these studies employed a low stringency initial 5 cycles, followed by 40 cycles at higher stringency. The rationale for using this program was two-fold. As these studies were designed to investigate the range of T cell receptors expressed in RA synovium, and all TCR V regions have not yet been sequenced, related TCR families which have sequences related to the primers used here may also be amplified in the initial low stringency cycles. 40 cycles of amplification were then used to amplify even low frequency transcripts. This should help overcome the potential problem of sampling error, which is possible from surgical specimens. Thus, if local accumulations of specific TCR bearing T cells are present, and such a local accumulation is missed in the surgical specimen, their presence still may be detected if they are also present at lower frequency in the surgical specimen examined. Preliminary experiments with these primers utilizing the program described in Materials and Methods revealed that all of them (except Vβ16) are effective in amplifying TCR V regions from PHA stimulated peripheral blood mononuclear cells, but that only the appropriate V region primers amplified Jurkat cell cDNA TCR ((20) and data not shown).

Synovial T Cells RNA was extracted and cDNA synthesized from both whole synovium and PHA stimulated/IL-2-maintained synovial T cell lines. Synovial T cell lines derived in this

manner have been previously described (17), and early on represent a phenotypically mixed population, including CD8+ and CD4+ cells (17). FACS analysis was available for 4 of these cell lines at the time of analysis, and the data is shown in Table 3. In 3 of these, CD4+ cells predominated, while in the other, CD8+ cells were more prevalent.

TABLE 3
PHENOTYPE OF SYNOVIAL TISSUE T CELL LINES

PATIENT	CONTROL	CD3+	CD4+	CD8+
EP_1	1%	90%	25%	54%
NJ_1	1%	80%	81%	9%
MW_1	1%	99%	77%	28%
HR_1	3%	98%	74%	15%

T cell receptor transcripts were amplified from cDNA derived from rheumatoid synovial T cell lines. All rheumatoid synovia were obtained at the time of joint surgery, and thus represented late disease. cDNA was split into equal portions and amplified with the middle constant region primers ($C\beta_{mid}$ or $C\alpha_{mid}$) in combination with each of the respective individual variable region primers noted in Fig. 5 (eg., $C\beta_{mid}$+Cβ1, $C\beta_{mid}$+Cβ2,...$C\beta_{mid}$+Cβ20; $C\alpha_{mid}$+Cα1; $C\alpha_{mid}$+Cα2, ...$C\alpha_{mid}$ + Cα18). Following electrophoresis and transfer, these were probed with Cβ5′ or Cα5′ respectively. The results for the synovial T cell lines is shown in Figure 2. An average of 15 alpha chain and 15.8 beta chain families were detected in these cell lines. This suggests that a quite heterogeneous population of T cells is present in synovium. However, as these cell lines were initially expanded with PHA, it is possible that the proportion of the various TCR subsets alter during culture. In addition, the ability of PHA to activate resting T cells raises concern about the relative proportion of activated T cells following stimulation compared with prior to stimulation. Therefore, similar analyses were performed on whole, unstimulated rheumatoid synovium.

Rheumatoid Synovium

The results for the whole synovia or freshly isolated, unstimulated synovial T cells analyzed similarly are

shown in Figure 3. An average of 4.2 alpha chain and 9.7 beta chain families were detected by this technique. The intensity of the bands detected is quite variable in Figure 2 & 3. To further evaluate the technique, cDNA was pooled from 4 synovia, and amplified with these primers for increasing numbers of cycles (Figure 4). Note that the intensity of some bands which appeared in early cycles faded relative to the intensity of bands which arose at later cycles. Thus, the intensity of the bands cannot be taken as an indicator of their relative abundance.

The frequency of occurrence of each TCR variable region was tabulated for synovial tissue in Figures 6 and 7. While the T cell receptor expression seen in the synovial T cell lines is quite heterogeneous, the expression in rheumatoid synovia was somewhat more limited. Specifically, Vα17 was present 7/10 synovia, and Vα1 was present in 5/10. Vβ14 was seen in 9/10 samples, while Vβ17 and Vβ12 were present in 8/10 specimens and Vβ7 was seen in 7/10. This suggests the presence of these variable regions in many rheumatoid synovia from many different patients. When analyzed statistically, the frequency of Vβ12, 14 & 17 were $\geq$2 standard errors above the mean values for all TCR Vβs detected, and Vα17 and $\geq$2 standard errors above the mean values for all TCR Vαa detected.

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SEQUENCE LISTING

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Weiner, David B.

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(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

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(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 237 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..237

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

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AAG AAG GAG CGC TTC TCC CTG ATT CTG GAG TCC GCC AGC ACC AAC CAG
Lys Lys Glu Arg Phe Ser Leu Ile Leu Glu Ser Ala Ser Thr Asn Gln
            20                  25                  30

ACA TCT ATG TAC CTC TGT GCC AGC AGT TCA CAA AAA CCC AAC AGT AAA
Thr Ser Met Tyr Leu Cys Ala Ser Ser Ser Gln Lys Pro Asn Ser Lys
        35                  40                  45

ACC TTC GGT TCG GGG ACC AGG TTG TCC GTT GTA GAG GAC CTG AAC AAG
Thr Phe Gly Ser Gly Thr Arg Leu Ser Val Val Glu Asp Leu Asn Lys
    50                  55                  60

GTG TTC CCA CCC GAG GTC GCT GTG TTT GAG CCA TCA GAA GCA GAG
Val Phe Pro Pro Glu Val Ala Val Phe Glu Pro Ser Glu Ala Glu
65                  70                  75
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(2) INFORMATION FOR SEQ ID NO:2:

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(A) LENGTH: 79 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

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 1               5                  10                  15

Lys Lys Glu Arg Phe Ser Leu Ile Leu Glu Ser Ala Ser Thr Asn Gln
            20                  25                  30

Thr Ser Met Tyr Leu Cys Ala Ser Ser Ser Gln Lys Pro Asn Ser Lys
        35                  40                  45

Thr Phe Gly Ser Gly Thr Arg Leu Ser Val Val Glu Asp Leu Asn Lys
    50                  55                  60

Val Phe Pro Pro Glu Val Ala Val Phe Glu Pro Ser Glu Ala Glu
65                  70                  75
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(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 231 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
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(B) LOCATION: 1..231

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

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AAG AAG GAG CGC TTC TCC CTG ATT CTG GAG TCC GCC AGC ACC AAC CAG
Lys Lys Glu Arg Phe Ser Leu Ile Leu Glu Ser Ala Ser Thr Asn Gln
            20                  25                  30

ACA TCT ATG TAC CTC TGT GCC AGC AGT TGG GGG ACT GAA GCT TTC TTT
Thr Ser Met Tyr Leu Cys Ala Ser Ser Trp Gly Thr Glu Ala Phe Phe
        35                  40                  45

GGA CAA GGC ACC AGA CTC ACA GTT GTA GAG GAC CTG AAC AAG GTG TTC
Gly Gln Gly Thr Arg Leu Thr Val Val Glu Asp Leu Asn Lys Val Phe
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(A) LENGTH: 77 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

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            20                  25                  30

Thr Ser Met Tyr Leu Cys Ala Ser Ser Trp Gly Thr Glu Ala Phe Phe
        35                  40                  45

Gly Gln Gly Thr Arg Leu Thr Val Val Glu Asp Leu Asn Lys Val Phe
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Pro Pro Glu Val Ala Val Phe Glu Pro Ser Glu Ala Glu
65                  70                  75
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(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 246 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..246

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

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Glu Thr Asp Lys Gly Asp Val Pro Glu Gly Tyr Ser Val Ser Arg Glu
  1               5                  10                  15

AAG AAG GAG CGC TTC TCC CTG ATT CTG GAG TCC GCC AGC ACC AAC CAG
Lys Lys Glu Arg Phe Ser Leu Ile Leu Glu Ser Ala Ser Thr Asn Gln
            20                  25                  30

ACA TCT ATG TAC CTC TGT GCC AGC AGT TTG CTC CAG CGG ACC ACC ACA
Thr Ser Met Tyr Leu Cys Ala Ser Ser Leu Leu Gln Arg Thr Thr Thr
        35                  40                  45

GAT ACG CAG TAT TTT GGC CCA GGC ACC CGG CTG ACA GTG CTC GAG GAC
Asp Thr Gln Tyr Phe Gly Pro Gly Thr Arg Leu Thr Val Leu Glu Asp
    50                  55                  60

CTG AAA AAC GTG TTC CCA CCC GAG ATC GCT GTG TTT GAG CCA TCA GAA
Leu Lys Asn Val Phe Pro Pro Glu Ile Ala Val Phe Glu Pro Ser Glu
65                  70                  75                  80

GCA GAG
Ala Glu
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(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 82 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Glu Thr Asp Lys Gly Asp Val Pro Glu Gly Tyr Ser Val Ser Arg Glu
1 5 10 15

Lys Lys Glu Arg Phe Ser Leu Ile Leu Glu Ser Ala Ser Thr Asn Gln
20 25 30

Thr Ser Met Tyr Leu Cys Ala Ser Ser Leu Leu Gln Arg Thr Thr Thr
35 40 45

Asp Thr Gln Tyr Phe Gly Pro Gly Thr Arg Leu Thr Val Leu Glu Asp
50 55 60

Leu Lys Asn Val Phe Pro Pro Glu Ile Ala Val Phe Glu Pro Ser Glu
65 70 75 80

Ala Glu

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 234 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..234

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

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GTG ACT GAT AAG GGA GAT GTT CCT GAA GGG TAC AGT GTC TCT AGA GAG
Val Thr Asp Lys Gly Asp Val Pro Glu Gly Tyr Ser Val Ser Arg Glu
  1               5                  10                  15

AAG AAG GAG CGC TTC TCC CTG ATT CTG GAG TCC GCC AGC ACC AAC CAG
Lys Lys Glu Arg Phe Ser Leu Ile Leu Glu Ser Ala Ser Thr Asn Gln
            20                  25                  30

ACA TCT ATG TAC CTC TGT GCC AGC AGC CTG GAC AGG GGC GAG CAG TAC
Thr Ser Met Tyr Leu Cys Ala Ser Ser Leu Asp Arg Gly Glu Gln Tyr
        35                  40                  45

TTC GGG CCG GGC ACC AGG CTC ACG GTC ACA GAG GAC CTG AAA AAC GTG
Phe Gly Pro Gly Thr Arg Leu Thr Val Thr Glu Asp Leu Lys Asn Val
    50                  55                  60

TTC CCA CCC GAG GTC GCT GTG TTT GAG CCA TCA GAA GCA GAG
Phe Pro Pro Glu Val Ala Val Phe Glu Pro Ser Glu Ala Glu
65                  70                  75
```

2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 78 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

```
Val Thr Asp Lys Gly Asp Val Pro Glu Gly Tyr Ser Val Ser Arg Glu
 1               5                  10                  15

Lys Lys Glu Arg Phe Ser Leu Ile Leu Glu Ser Ala Ser Thr Asn Gln
            20                  25                  30

Thr Ser Met Tyr Leu Cys Ala Ser Ser Leu Asp Arg Gly Glu Gln Tyr
        35                  40                  45

Phe Gly Pro Gly Thr Arg Leu Thr Val Thr Glu Asp Leu Lys Asn Val
    50                  55                  60

Phe Pro Pro Glu Val Ala Val Phe Glu Pro Ser Glu Ala Glu
65                  70                  75
```

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 240 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..240

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

```
GTG ACT GAT AAG GGA GAT GTT CCT GAA GGG TAC AGT GTC TCT AGA GAG
Val Thr Asp Lys Gly Asp Val Pro Glu Gly Tyr Ser Val Ser Arg Glu
```

```
 1               5                  10                  15

AAG AAG GAG CGC TTC TCC CTG ATT CTG GAG TCC GCC AGC ACC AAC CAG
Lys Lys Glu Arg Phe Ser Leu Ile Leu Glu Ser Ala Ser Thr Asn Gln
            20                  25                  30

ACA TCT ATG TAC CTC TGT GCC AGC AGT TTA ACC TCC GTC ACA GAT ACG
Thr Ser Met Tyr Leu Cys Ala Ser Ser Leu Thr Ser Val Thr Asp Thr
        35                  40                  45

CAG TAT TTT GGC CCA GGC ACC CGG CTG ACA GTG CTC GAG GAC CTG AAA
Gln Tyr Phe Gly Pro Gly Thr Arg Leu Thr Val Leu Glu Asp Leu Lys
    50                  55                  60

AAC GTG TTC CCA CCC GAG GTC GCT GTG TTT GAG CCA TCA GAA GCA GAG
Asn Val Phe Pro Pro Glu Val Ala Val Phe Glu Pro Ser Glu Ala Glu
65                  70                  75                  80
```

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 80 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

```
Val Thr Asp Lys Gly Asp Val Pro Glu Gly Tyr Ser Val Ser Arg Glu
 1               5                  10                  15

Lys Lys Glu Arg Phe Ser Leu Ile Leu Glu Ser Ala Ser Thr Asn Gln
            20                  25                  30
```

```
Thr Ser Met Tyr Leu Cys Ala Ser Ser Leu Thr Ser Val Thr Asp Thr
        35                  40                  45

Gln Tyr Phe Gly Pro Gly Thr Arg Leu Thr Val Leu Glu Asp Leu Lys
    50                  55                  60

Asn Val Phe Pro Pro Glu Val Ala Val Phe Glu Pro Ser Glu Ala Glu
65                  70                  75                  80
```

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 252 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..252

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

```
TTT CAG AAA GGA GAT ATA GCT GAA GGG TAC AGC GTC TCT CGG GAG AAG
Phe Gln Lys Gly Asp Ile Ala Glu Gly Tyr Ser Val Ser Arg Glu Lys
 1               5                  10                  15

AAG GAA TCC TTT CCT CTC ACT GTG ACA TCG GCC CAA AAG AAC CCG ACA
Lys Glu Ser Phe Pro Leu Thr Val Thr Ser Ala Gln Lys Asn Pro Thr
            20                  25                  30

GCT TTC TAT CTC TGT GCC AGT AGT ATT GGG GGA CAA GGG CTA ACC GGG
Ala Phe Tyr Leu Cys Ala Ser Ser Ile Gly Gly Gln Gly Leu Thr Gly
```

```
         35                  40                  45

GCC AAA AAC ATT CAG TAC TTC GGC GCC GGG ACC CGG CCC TCA GTG CTG
Ala Lys Asn Ile Gln Tyr Phe Gly Ala Gly Thr Arg Pro Ser Val Leu
     50                  55                  60

GAG GAC CTG AAA AAC GTG TTC CCA CCC GAG GTC GCT GTG TTT GAG CCA
Glu Asp Leu Lys Asn Val Phe Pro Pro Glu Val Ala Val Phe Glu Pro
 65                  70                  75                  80

TCA GAA GCA GAG
Ser Glu Ala Glu
```

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 84 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

```
Phe Gln Lys Gly Asp Ile Ala Glu Gly Tyr Ser Val Ser Arg Glu Lys
  1               5                  10                  15

Lys Glu Ser Phe Pro Leu Thr Val Thr Ser Ala Gln Lys Asn Pro Thr
             20                  25                  30

Ala Phe Tyr Leu Cys Ala Ser Ser Ile Gly Gly Gln Gly Leu Thr Gly
         35                  40                  45

Ala Lys Asn Ile Gln Tyr Phe Gly Ala Gly Thr Arg Pro Ser Val Leu
     50                  55                  60
```

```
Glu Asp Leu Lys Asn Val Phe Pro Pro Glu Val Ala Val Phe Glu Pro
 65                  70                  75                  80

Ser Glu Ala Glu
```

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 237 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..237

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

```
TTT CAG AAA GGA GAT ATA GCT GAA GGG TAC AAA GTC TCT CGA AAA GAG
Phe Gln Lys Gly Asp Ile Ala Glu Gly Tyr Lys Val Ser Arg Lys Glu
  1               5                  10                  15

AAG AGG AAT TTC CCC CTG ATC CTG GAG TCG CCC AGC CCC AAC CAG ACC
Lys Arg Asn Phe Pro Leu Ile Leu Glu Ser Pro Ser Pro Asn Gln Thr
            20                  25                  30

TCT CTG TAC TTC TGT GCC AGC AGT TTG GGG GGA ACC TAC AAT GAG CAG
Ser Leu Tyr Phe Cys Ala Ser Ser Leu Gly Gly Thr Tyr Asn Glu Gln
        35                  40                  45

TTC TTC GGG CCA GGG ACA CGG CTC ACC GTG CTA GAG GAC CTG AAA AAC
Phe Phe Gly Pro Gly Thr Arg Leu Thr Val Leu Glu Asp Leu Lys Asn
```

```
     50                  55                  60

GTG TTC CCA CCC GAG GTC GCT GTG TTT GAG CCA TCA GAA GCA GAG
Val Phe Pro Pro Glu Val Ala Val Phe Glu Pro Ser Glu Ala Glu
 65                  70                  75
```

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 79 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

```
Phe Gln Lys Gly Asp Ile Ala Glu Gly Tyr Lys Val Ser Arg Lys Glu
  1               5                  10                  15

Lys Arg Asn Phe Pro Leu Ile Leu Glu Ser Pro Ser Pro Asn Gln Thr
             20                  25                  30

Ser Leu Tyr Phe Cys Ala Ser Ser Leu Gly Gly Thr Tyr Asn Glu Gln
         35                  40                  45

Phe Phe Gly Pro Gly Thr Arg Leu Thr Val Leu Glu Asp Leu Lys Asn
     50                  55                  60

Val Phe Pro Pro Glu Val Ala Val Phe Glu Pro Ser Glu Ala Glu
 65                  70                  75
```

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 342 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..342

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

```
CTG AGG TGC AAC TAT TCC TAT GGG GCA ACA CCT TAT CTC TTC TGG TAT
Leu Arg Cys Asn Tyr Ser Tyr Gly Ala Thr Pro Tyr Leu Phe Trp Tyr
 1               5                  10                  15

GTC CAG TCC CCC GGC CAA GGC CTC CAG CTG CCC CTG AAG TAC TTT TCA
Val Gln Ser Pro Gly Gln Gly Leu Gln Leu Pro Leu Lys Tyr Phe Ser
            20                  25                  30

GGA GAC ACT CTG GTT CAA GGC ATT AAA GGC TTT GAG GCT GAA TTT AAG
Gly Asp Thr Leu Val Gln Gly Ile Lys Gly Phe Glu Ala Glu Phe Lys
        35                  40                  45

AGG AGT CAA TCT TCC TTC AAT CTG AGG AAA CCC TCT GTG CAT TGG AGT
Arg Ser Gln Ser Ser Phe Asn Leu Arg Lys Pro Ser Val His Trp Ser
    50                  55                  60

GAT GCT GCT GAG TAC TTC TGT GCT GTG GGT GCT GAT TCA GGA TAC AGC
Asp Ala Ala Glu Tyr Phe Cys Ala Val Gly Ala Asp Ser Gly Tyr Ser
65                  70                  75                  80

ACC CTC ACC TTT GGG AAG GGG ACT ATG CTT CTA GTC TCT CCA GAT ATC
Thr Leu Thr Phe Gly Lys Gly Thr Met Leu Leu Val Ser Pro Asp Ile
```

```
                  85                  90                  95

CAG AAC CCT GAC CCT GCC GTG TAC CAG CTG AGA GAC TCT AAA TCC AGT
Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp Ser Lys Ser Ser
            100                 105                 110

GAC AAG
Asp Lys
```

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 114 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

```
Leu Arg Cys Asn Tyr Ser Tyr Gly Ala Thr Pro Tyr Leu Phe Trp Tyr
 1               5                  10                  15

Val Gln Ser Pro Gly Gln Gly Leu Gln Leu Pro Leu Lys Tyr Phe Ser
            20                  25                  30

Gly Asp Thr Leu Val Gln Gly Ile Lys Gly Phe Glu Ala Glu Phe Lys
        35                  40                  45

Arg Ser Gln Ser Ser Phe Asn Leu Arg Lys Pro Ser Val His Trp Ser
    50                  55                  60

Asp Ala Ala Glu Tyr Phe Cys Ala Val Gly Ala Asp Ser Gly Tyr Ser
65                  70                  75                  80
```

```
Thr Leu Thr Phe Gly Lys Gly Thr Met Leu Leu Val Ser Pro Asp Ile
                  85                  90                  95

Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp Ser Lys Ser Ser
            100                 105                 110

Asp Lys
```

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 336 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..336

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

```
CTG AGG TGC AAC TAT TCC TAT GGG GCA ACA CCT TAT CTC TTC TGG TAT
Leu Arg Cys Asn Tyr Ser Tyr Gly Ala Thr Pro Tyr Leu Phe Trp Tyr
  1               5                  10                  15

GTC CAG TCC CCC GGC CAA GGC CTC CAG CTG CTC CTG AAG TAC TTT TCA
Val Gln Ser Pro Gly Gln Gly Leu Gln Leu Leu Leu Lys Tyr Phe Ser
            20                  25                  30

GGA GAC ACT CTG GTT CAA GGC ATT AAA GGC TTT GAG GCT GAA TTT AAG
```

```
Gly Asp Thr Leu Val Gln Gly Ile Lys Gly Phe Glu Ala Glu Phe Lys
          35                  40                  45

AGG AGT CAA TCT TCC TTC AAT CTG AGG AAA CCC TCT GTG CAT TGG AGT
Arg Ser Gln Ser Ser Phe Asn Leu Arg Lys Pro Ser Val His Trp Ser
     50                  55                  60

GAT GCT GCT GAG TAC TTC TGT GCT GTG GGT CCC ACC CAC AAT GAC ATG
Asp Ala Ala Glu Tyr Phe Cys Ala Val Gly Pro Thr His Asn Asp Met
 65                  70                  75                  80

CGC TTT GGA GCA GGG ACC AGA CTG ACA GTA AAA CCA AAT ATC CAG AAC
Arg Phe Gly Ala Gly Thr Arg Leu Thr Val Lys Pro Asn Ile Gln Asn
                 85                  90                  95

CCT GAC CCT GCC GTG TAC CAG CTG AGA GAC TCT AAA TCC AGT GAC AAG
Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys
            100                 105                 110
```

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 112 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

```
Leu Arg Cys Asn Tyr Ser Tyr Gly Ala Thr Pro Tyr Leu Phe Trp Tyr
 1               5                  10                  15

Val Gln Ser Pro Gly Gln Gly Leu Gln Leu Leu Leu Lys Tyr Phe Ser
            20                  25                  30

Gly Asp Thr Leu Val Gln Gly Ile Lys Gly Phe Glu Ala Glu Phe Lys
        35                  40                  45

Arg Ser Gln Ser Ser Phe Asn Leu Arg Lys Pro Ser Val His Trp Ser
    50                  55                  60

Asp Ala Ala Glu Tyr Phe Cys Ala Val Gly Pro Thr His Asn Asp Met
65                  70                  75                  80

Arg Phe Gly Ala Gly Thr Arg Leu Thr Val Lys Pro Asn Ile Gln Asn
                85                  90                  95

Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys
            100                 105                 110
```

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 324 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

(A) NAME/KEY: CDS
(B) LOCATION: 1..324

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

```
CTG AGG TGC AAC TAT TCC TAT TCT GGG AGT CCT GAA CTC TTC TGG TAT
Leu Arg Cys Asn Tyr Ser Tyr Ser Gly Ser Pro Glu Leu Phe Trp Tyr
  1               5                  10                  15

GTC CAG TAC TCC AGA CAA CGC CTC CAG TTA CTC TTG AGA CAC ATC TCT
Val Gln Tyr Ser Arg Gln Arg Leu Gln Leu Leu Leu Arg His Ile Ser
            20                  25                  30

AGA GAG AGC ATC AAA GGC TTC ACT GCT GAC CTT AAC AAA GGC GAG ACA
Arg Glu Ser Ile Lys Gly Phe Thr Ala Asp Leu Asn Lys Gly Glu Thr
        35                  40                  45

TCT TTC CAC CTG AAG AAA CCA TTT GCT CAA GAG GAA GAC TCA GCC ATG
Ser Phe His Leu Lys Lys Pro Phe Ala Gln Glu Glu Asp Ser Ala Met
    50                  55                  60

TAT TAC TGT GCT CTA GCG CTG CAG GCA ACA AGC TTA CTT TTG GAG GAG
Tyr Tyr Cys Ala Leu Ala Leu Gln Ala Thr Ser Leu Leu Leu Glu Glu
65                  70                  75                  80

GAA CCC AGG GTG CTA GTT AAA CCA AAT ATC CAG AAC CCT GAC CCT GCC
Glu Pro Arg Val Leu Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala
                85                  90                  95

GTG TAC CAG CTG AGA GAC TCT AAA TCC AGT GAC AAG
Val Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys
            100                 105
```

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 108 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

```
Leu Arg Cys Asn Tyr Ser Tyr Ser Gly Ser Pro Glu Leu Phe Trp Tyr
 1               5                  10                  15

Val Gln Tyr Ser Arg Gln Arg Leu Gln Leu Leu Leu Arg His Ile Ser
            20                  25                  30

Arg Glu Ser Ile Lys Gly Phe Thr Ala Asp Leu Asn Lys Gly Glu Thr
        35                  40                  45

Ser Phe His Leu Lys Lys Pro Phe Ala Gln Glu Glu Asp Ser Ala Met
    50                  55                  60

Tyr Tyr Cys Ala Leu Ala Leu Gln Ala Thr Ser Leu Leu Leu Glu Glu
65                  70                  75                  80

Glu Pro Arg Val Leu Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala
                85                  90                  95

Val Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys
            100                 105
```

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 352 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 2..352

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

```
C TTG TCA CTG GAT TTA GAG TCT CTC AGC TGC AGT TAC ACA GTC AGC
  Leu Ser Leu Asp Leu Glu Ser Leu Ser Cys Ser Tyr Thr Val Ser
    1               5                  10                  15

GGT TTA AGA GGG CTG TTC TGG TAT AGG CAA GAT CCT GGG AAA GGC CCT
Gly Leu Arg Gly Leu Phe Trp Tyr Arg Gln Asp Pro Gly Lys Gly Pro
                20                  25                  30

GAA TTC CTC TTC ACC CTG TAT TCA GCT GGG GAA GAA AAG GAG AAA GAA
Glu Phe Leu Phe Thr Leu Tyr Ser Ala Gly Glu Glu Lys Glu Lys Glu
            35                  40                  45

AGG CTA AAA GCC ACA TTA ACA AAG AAG GAA AGC TTT CTG CAC ATC ACA
Arg Leu Lys Ala Thr Leu Thr Lys Lys Glu Ser Phe Leu His Ile Thr
        50                  55                  60

GCC CCT AAA CCT GAA GAC TCA GCC ACT TAT CTC TGT GCT GCG AGG CGA
```

```
Ala Pro Lys Pro Glu Asp Ser Ala Thr Tyr Leu Cys Ala Ala Arg Arg
     65                  70                  75

TCA GAT GGC CAG AAG CTG CTC TTT GCA AGG GGA ACC ATG TTA AAG GTG
Ser Asp Gly Gln Lys Leu Leu Phe Ala Arg Gly Thr Met Leu Lys Val
 80                  85                  90                  95

GAT CTT AAT ATC CAG AAC CCT GAC CCT GCC GTG TAC CAG CTG AGA GAC
Asp Leu Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp
                100                 105                 110

TCT AAA TCC AGT GAC AAG
Ser Lys Ser Ser Asp Lys
            115
```

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 117 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

```
Leu Ser Leu Asp Leu Glu Ser Leu Ser Cys Ser Tyr Thr Val Ser Gly
  1               5                  10                  15

Leu Arg Gly Leu Phe Trp Tyr Arg Gln Asp Pro Gly Lys Gly Pro Glu
            20                  25                  30

Phe Leu Phe Thr Leu Tyr Ser Ala Gly Glu Glu Lys Glu Lys Glu Arg
        35                  40                  45
```

```
Leu Lys Ala Thr Leu Thr Lys Lys Glu Ser Phe Leu His Ile Thr Ala
     50                  55                  60

Pro Lys Pro Glu Asp Ser Ala Thr Tyr Leu Cys Ala Ala Arg Arg Ser
 65                  70                  75                  80

Asp Gly Gln Lys Leu Leu Phe Ala Arg Gly Thr Met Leu Lys Val Asp
                 85                  90                  95

Leu Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp Ser
            100                 105                 110

Lys Ser Ser Asp Lys
        115
```

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 352 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 2..352

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

```
C TTG TCA CTG GAT TTA GAG TCT CTC AGC TGC AGT TAC ACA GTC AGC
  Leu Ser Leu Asp Leu Glu Ser Leu Ser Cys Ser Tyr Thr Val Ser
```

```
    1               5                  10                  15

GGT TTA AGA GGG CTG TTC TGG TAT AGG CAA GAT CCT GGG AAA GGC CCT
Gly Leu Arg Gly Leu Phe Trp Tyr Arg Gln Asp Pro Gly Lys Gly Pro
                20                  25                  30

GAA TTC CTC TTC ACC CTG TAT TCA GCT GGG GAA GAA AAG GAG AAA GAA
Glu Phe Leu Phe Thr Leu Tyr Ser Ala Gly Glu Glu Lys Glu Lys Glu
            35                  40                  45

AGG CTA AAA GCC ACA TTA ACA AAG AAG GAA AGC TTT CTG CAC ATC ACA
Arg Leu Lys Ala Thr Leu Thr Lys Lys Glu Ser Phe Leu His Ile Thr
        50                  55                  60

GCC CCT AAA CCT GAA GAC TCA GCC ACT TAT CTC TGT GCT GTG AGG CGA
Ala Pro Lys Pro Glu Asp Ser Ala Thr Tyr Leu Cys Ala Val Arg Arg
    65                  70                  75

TCA GAT GGC CAG AAG CTG CTC TTT GCA AGG GGA ACC ATG TTA AAG GTG
Ser Asp Gly Gln Lys Leu Leu Phe Ala Arg Gly Thr Met Leu Lys Val
80                  85                  90                  95

GAT CTT AAT ATC CAG AAC CCT GAC CCT GCC GTG TAC CAG CTG AGA GAC
Asp Leu Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp
                100                 105                 110

TCT AAA TCC AGT GAC AAG
Ser Lys Ser Ser Asp Lys
            115
```

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 117 amino acids
(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

```
Leu Ser Leu Asp Leu Glu Ser Leu Ser Cys Ser Tyr Thr Val Ser Gly
 1               5                  10                  15

Leu Arg Gly Leu Phe Trp Tyr Arg Gln Asp Pro Gly Lys Gly Pro Glu
            20                  25                  30

Phe Leu Phe Thr Leu Tyr Ser Ala Gly Glu Glu Lys Glu Lys Glu Arg
        35                  40                  45

Leu Lys Ala Thr Leu Thr Lys Lys Glu Ser Phe Leu His Ile Thr Ala
    50                  55                  60

Pro Lys Pro Glu Asp Ser Ala Thr Tyr Leu Cys Ala Val Arg Arg Ser
65                  70                  75                  80

Asp Gly Gln Lys Leu Leu Phe Ala Arg Gly Thr Met Leu Lys Val Asp
                85                  90                  95

Leu Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp Ser
            100                 105                 110

Lys Ser Ser Asp Lys
        115
```

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 352 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: double
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 2..352

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

```
C TTG TCA CTG GAT TTA GAG TCT CTC AGC TGC AGT TAC ACA GTC AGC
  Leu Ser Leu Asp Leu Glu Ser Leu Ser Cys Ser Tyr Thr Val Ser
    1               5                  10                  15

GGT TTA AGA GGG CTG TTC TGG TAT AGG CAA GAT CCT GGG AAA GGC CCT
Gly Leu Arg Gly Leu Phe Trp Tyr Arg Gln Asp Pro Gly Lys Gly Pro
                20                  25                  30

GAA TTC CTC TTC ACC CTG TAT TCA GCT GGG GAA GAA AAG GAG AAA GAA
Glu Phe Leu Phe Thr Leu Tyr Ser Ala Gly Glu Glu Lys Glu Lys Glu
            35                  40                  45

AGG CTA AAA GCC ACA TTA ACA AAG AAG GAA AGC TTT CTG CAC ATC ACA
Arg Leu Lys Ala Thr Leu Thr Lys Lys Glu Ser Phe Leu His Ile Thr
        50                  55                  60

GCC CCT AAA CCT GAA GAC TCA GCC ACT TAT CTC TGT GCT GTG AGG CGA
Ala Pro Lys Pro Glu Asp Ser Ala Thr Tyr Leu Cys Ala Val Arg Arg
    65                  70                  75
```

```
TCA GAT GGC CAG AAG CTG CTC TTT GCA AGG GGA ACC ATG TTA AAG GTG
Ser Asp Gly Gln Lys Leu Leu Phe Ala Arg Gly Thr Met Leu Lys Val
 80                  85                  90                  95

GAT CTT AAT ATC CAG AAC CCT GAC CCT GCC GTG TAC CAG CTG AGA GAC
Asp Leu Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp
                100                 105                 110

TCT AAA TCC AGT GAC AAG
Ser Lys Ser Ser Asp Lys
            115
```

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 117 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

```
Leu Ser Leu Asp Leu Glu Ser Leu Ser Cys Ser Tyr Thr Val Ser Gly
  1               5                  10                  15

Leu Arg Gly Leu Phe Trp Tyr Arg Gln Asp Pro Gly Lys Gly Pro Glu
            20                  25                  30

Phe Leu Phe Thr Leu Tyr Ser Ala Gly Glu Glu Lys Glu Lys Glu Arg
        35                  40                  45

Leu Lys Ala Thr Leu Thr Lys Lys Glu Ser Phe Leu His Ile Thr Ala
    50                  55                  60
```

Pro Lys Pro Glu Asp Ser Ala Thr Tyr Leu Cys Ala Val Arg Arg Ser
65 70 75 80

Asp Gly Gln Lys Leu Leu Phe Ala Arg Gly Thr Met Leu Lys Val Asp
85 90 95

Leu Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp Ser
100 105 110

Lys Ser Ser Asp Lys
115

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 352 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 2..352

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

C TTG TCA CTG GAT TTA GAG TCT CTC AGC TGC AGT TAC ACA GTC AGC
Leu Ser Leu Asp Leu Glu Ser Leu Ser Cys Ser Tyr Thr Val Ser
1 5 10 15

GGT TTA AGA TGG CTG TTC TGG TAT AGG CAA GAT CCT GGG AAA GGC CCT

```
Gly Leu Arg Trp Leu Phe Trp Tyr Arg Gln Asp Pro Gly Lys Gly Pro
                  20                  25                  30

GAA TTC CTC TTC GCC CTG TAT TCA GCT GGG GAA GAA AAG GAG AAA GAA
Glu Phe Leu Phe Ala Leu Tyr Ser Ala Gly Glu Glu Lys Glu Lys Glu
             35                  40                  45

AGG CTA AAA GCC ACA TTA ACA AAG AAG GAA AGC TTT CTG CAC ATC ACA
Arg Leu Lys Ala Thr Leu Thr Lys Lys Glu Ser Phe Leu His Ile Thr
         50                  55                  60

GCC CCT AAA CCT GAA GAC TCA GCC ACT TAT CTC TGT GCT GTG AGG CGA
Ala Pro Lys Pro Glu Asp Ser Ala Thr Tyr Leu Cys Ala Val Arg Arg
     65                  70                  75

TCA GAT GGC CAG AAG CTG CTC TTT GCA AGG GGA ACC ATG TTA AAG GTG
Ser Asp Gly Gln Lys Leu Leu Phe Ala Arg Gly Thr Met Leu Lys Val
 80                  85                  90                  95

GAT CTT AAT ATC CAG AAC CCT GAC CCT GCC GTG TAC CAG CTG AGA GAC
Asp Leu Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp
                 100                 105                 110

TCT AAA TCC AGT GAC AAG
Ser Lys Ser Ser Asp Lys
             115
```

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 117 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

```
Leu Ser Leu Asp Leu Glu Ser Leu Ser Cys Ser Tyr Thr Val Ser Gly
 1               5                  10                  15

Leu Arg Trp Leu Phe Trp Tyr Arg Gln Asp Pro Gly Lys Gly Pro Glu
            20                  25                  30

Phe Leu Phe Ala Leu Tyr Ser Ala Gly Glu Glu Lys Glu Lys Glu Arg
        35                  40                  45

Leu Lys Ala Thr Leu Thr Lys Lys Glu Ser Phe Leu His Ile Thr Ala
    50                  55                  60

Pro Lys Pro Glu Asp Ser Ala Thr Tyr Leu Cys Ala Val Arg Arg Ser
65                  70                  75                  80

Asp Gly Gln Lys Leu Leu Phe Ala Arg Gly Thr Met Leu Lys Val Asp
                85                  90                  95

Leu Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp Ser
            100                 105                 110

Lys Ser Ser Asp Lys
        115
```

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 343 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 2..343

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

```
A GAT GTC TCC ATG AAC TGC ACT TCT TCA AGC ATA TTT AAC ACC TGG
  Asp Val Ser Met Asn Cys Thr Ser Ser Ser Ile Phe Asn Thr Trp
    1               5                  10                  15

CTA TGG TAC AAG CAG GAC CCT GGG GAA GGT CCT GTC CTC TTG ATA GCC
Leu Trp Tyr Lys Gln Asp Pro Gly Glu Gly Pro Val Leu Leu Ile Ala
                20                  25                  30

TTA TAT AAG GCT GGT GAA TTG ACC TCA AAT GGA AGA CTG ACT GCT CAG
Leu Tyr Lys Ala Gly Glu Leu Thr Ser Asn Gly Arg Leu Thr Ala Gln
            35                  40                  45

TTT GGT ATA ACC AGA AAG GAC AGC TTC CTG AAT ATC TCA GCA TCC ATA
Phe Gly Ile Thr Arg Lys Asp Ser Phe Leu Asn Ile Ser Ala Ser Ile
        50                  55                  60

CCT AGT GAT GTA GGC ATC TAC TTC TGT GCT GGG CAG GCC CTC ACC GGT
Pro Ser Asp Val Gly Ile Tyr Phe Cys Ala Gly Gln Ala Leu Thr Gly
    65                  70                  75

AAC CAG TTC TAT TTT GGG ACA GGG ACA AGT TTG ACG GTC ATT CCA AAT
Asn Gln Phe Tyr Phe Gly Thr Gly Thr Ser Leu Thr Val Ile Pro Asn
80                  85                  90                  95
```

```
ATC CAG AAC CCT GAC CCT GCC GTG TAC CAG CTG AGA GAC TCT AAA TCC
Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp Ser Lys Ser
                100                 105                 110

AGT GAC AAG
Ser Asp Lys
```

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 114 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

```
Asp Val Ser Met Asn Cys Thr Ser Ser Ser Ile Phe Asn Thr Trp Leu
 1               5                  10                  15

Trp Tyr Lys Gln Asp Pro Gly Glu Gly Pro Val Leu Leu Ile Ala Leu
            20                  25                  30

Tyr Lys Ala Gly Glu Leu Thr Ser Asn Gly Arg Leu Thr Ala Gln Phe
        35                  40                  45

Gly Ile Thr Arg Lys Asp Ser Phe Leu Asn Ile Ser Ala Ser Ile Pro
    50                  55                  60

Ser Asp Val Gly Ile Tyr Phe Cys Ala Gly Gln Ala Leu Thr Gly Asn
65                  70                  75                  80

Gln Phe Tyr Phe Gly Thr Gly Thr Ser Leu Thr Val Ile Pro Asn Ile
                85                  90                  95
```

```
Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp Ser Lys Ser Ser
            100                 105                 110

Asp Lys
```

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 408 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..408

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

```
CTT GTC ACT GGA TTT AGA GTC TCT CAG CTG GTG GAG CAG AGC CCT CAA
Leu Val Thr Gly Phe Arg Val Ser Gln Leu Val Glu Gln Ser Pro Gln
  1               5                  10                  15

TCT TTG ATA GTC CAG AAA GGA GGG ATT TCA ATT ATA AAC TGT GCT TAT
Ser Leu Ile Val Gln Lys Gly Gly Ile Ser Ile Ile Asn Cys Ala Tyr
            20                  25                  30

GAG AAC ACT GCG TTT GAC TAC TTT CCA TGG TAC CAA CAA TTC CCT GGG
Glu Asn Thr Ala Phe Asp Tyr Phe Pro Trp Tyr Gln Gln Phe Pro Gly
        35                  40                  45
```

```
AAA GGC CCT GCA TTA TTG ATA GCC ATA CGT CCA GAT GTG AGT GAA AAG
Lys Gly Pro Ala Leu Leu Ile Ala Ile Arg Pro Asp Val Ser Glu Lys
     50                  55                  60

AAA GAA GGA AGA TTC ACA ATC TCC TTC AAT AAA AGT GCC AAG CAG TTC
Lys Glu Gly Arg Phe Thr Ile Ser Phe Asn Lys Ser Ala Lys Gln Phe
 65                  70                  75                  80

TCA TTG CAT ATC ATG GAT TCC CAG CCT GGA GAC TCA GCC ACC TAC TTC
Ser Leu His Ile Met Asp Ser Gln Pro Gly Asp Ser Ala Thr Tyr Phe
                 85                  90                  95

TGT GCA GCA GAG GGA GGA AAG CTT ATC TTC GGA CAG GGA ACG GAG TTA
Cys Ala Ala Glu Gly Gly Lys Leu Ile Phe Gly Gln Gly Thr Glu Leu
            100                 105                 110

TCT GTG AAA CCC AAT ATC CAG AAC CCT GAC CCT GCC GTG TAC CAG CTG
Ser Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu
        115                 120                 125

AGA GAC TCT AAA TCC AGT GAC AAG
Arg Asp Ser Lys Ser Ser Asp Lys
    130                 135
```

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 136 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

```
Leu Val Thr Gly Phe Arg Val Ser Gln Leu Val Glu Gln Ser Pro Gln
 1               5                  10                  15

Ser Leu Ile Val Gln Lys Gly Gly Ile Ser Ile Ile Asn Cys Ala Tyr
            20                  25                  30

Glu Asn Thr Ala Phe Asp Tyr Phe Pro Trp Tyr Gln Gln Phe Pro Gly
        35                  40                  45

Lys Gly Pro Ala Leu Leu Ile Ala Ile Arg Pro Asp Val Ser Glu Lys
    50                  55                  60

Lys Glu Gly Arg Phe Thr Ile Ser Phe Asn Lys Ser Ala Lys Gln Phe
65                  70                  75                  80

Ser Leu His Ile Met Asp Ser Gln Pro Gly Asp Ser Ala Thr Tyr Phe
                85                  90                  95

Cys Ala Ala Glu Gly Gly Lys Leu Ile Phe Gly Gln Gly Thr Glu Leu
            100                 105                 110

Ser Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu
        115                 120                 125

Arg Asp Ser Lys Ser Ser Asp Lys
    130                 135
```

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 240 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: double
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..240

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

```
TTT CAG AAA GGA GAT ATA GCT GAA GGG TAC AAA GTC TCT CGA AAA GAG
Phe Gln Lys Gly Asp Ile Ala Glu Gly Tyr Lys Val Ser Arg Lys Glu
 1               5                  10                  15

AAG AGG AAT TTC CCC CTG ATC CTG GAG TCG CCC AGC CCC AAC CAG ACC
Lys Arg Asn Phe Pro Leu Ile Leu Glu Ser Pro Ser Pro Asn Gln Thr
            20                  25                  30

TCT CTG TAC TTC TGT GCC AGC AGT CCG TTC TCT CGA GCA TCC TAT GGC
Ser Leu Tyr Phe Cys Ala Ser Ser Pro Phe Ser Arg Ala Ser Tyr Gly
        35                  40                  45

TAC ACC TTC GGT TCG GGG AAC AGG TTA ACC GTT GTA GAG GAC CTG AAA
Tyr Thr Phe Gly Ser Gly Asn Arg Leu Thr Val Val Glu Asp Leu Lys
    50                  55                  60

AAC GTG TTC CCA CCC GAG GTC GCT GTG TTT GAG CCA TCA GAA GCA GAG
Asn Val Phe Pro Pro Glu Val Ala Val Phe Glu Pro Ser Glu Ala Glu
65                  70                  75                  80
```

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 80 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

```
Phe Gln Lys Gly Asp Ile Ala Glu Gly Tyr Lys Val Ser Arg Lys Glu
 1               5                  10                  15

Lys Arg Asn Phe Pro Leu Ile Leu Glu Ser Pro Ser Pro Asn Gln Thr
            20                  25                  30

Ser Leu Tyr Phe Cys Ala Ser Ser Pro Phe Ser Arg Ala Ser Tyr Gly
        35                  40                  45

Tyr Thr Phe Gly Ser Gly Asn Arg Leu Thr Val Val Glu Asp Leu Lys
    50                  55                  60

Asn Val Phe Pro Pro Glu Val Ala Val Phe Glu Pro Ser Glu Ala Glu
65                  70                  75                  80
```

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

CTGAGGTGCA ACTACTCA

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

GTGTTCCCAG AGGGAGCCAT TGCC

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

GGTGAACAGT CAACAGGGAG A

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

ACAAGCATTA CTGTACTCCT A

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

GGCCCTGAAC ATTCAGGA

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

GTCACTTTCT AGCCTGCTGA

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

AGGAGCCATT GTCCAGATAA A

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

GGAGAGAATG TGGAGCAGCA TC

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs

(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

ATCTCAGTGC TTGTGATAAT A

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

ACCCAGCTGG TGGAGCAGAG CCCT

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

AGAAAGCAAG GACCAAGTGT T

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

CAGAAGGTAA CTCAAGCGCA GACT

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

GCTTATGAGA ACACTGCGT

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

GCAGCTTCCC TTCCAGCAAT

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

AGAACCTGAC TGCCCAGGAA

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

CATCTCCATG GACTCATATG A

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

GACTATACTA ACAGCATGT

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

TGTCAGGCAA TGACAAGG 18

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

AATAGGTCGA GACACTTGTC ACTGGA

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

CTTGTCACTG GATTTAGATC TCTCAGCTG

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

GTACACGGCA GGGTCAGGGT TCTGGATATT

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

AAGAGAGAGC AAAAGGAAAC ATTCTTGAAC

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

GCTGCAAGGC CACATACGAG CAAGGCGTCG

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

AAAATGAAAG AAAAACCAGA TATTCCTGAG

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

CTGAGGCCAC ATATGAGAGT GGATTTGTCA

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

CAGAGAAACA AAGGAAACTT CCCTGGTCGA

(2) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

GGGTGCGGCA GATGACTCAG GGCTGCCCAA

(2) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

ATAAATGAAA GTGTGCCAAG TCGCTTCTCA

(2) INFORMATION FOR SEQ ID NO:63:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

AACGTTCCGA TAGATGATTC AGGGATGCCC

(2) INFORMATION FOR SEQ ID NO:64:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

CATTATAAAT GAAACAGTTC CAAATCGCTT

(2) INFORMATION FOR SEQ ID NO:65:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

CTTATTCAGA AAGCAGAAAT AATCAATGAG

(2) INFORMATION FOR SEQ ID NO:66:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

TCCACAGAGA AGGGAGATCT TTCCTCTGAG

(2) INFORMATION FOR SEQ ID NO:67:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

GATACTGACA AAGGAGAAGT CTCAGATGGC

(2) INFORMATION FOR SEQ ID NO:68:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

GTGACTGATA AGGGAGATGT TCCTGAAGGG

(2) INFORMATION FOR SEQ ID NO:69:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

GATATAAACA AAGGAGAGAT CTCTGATGGA

(2) INFORMATION FOR SEQ ID NO:70:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

CATGATAATC TTTATCGACG TGTTATGGGA

(2) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

TTTCAGAAAG GAGATATAGC TGAAGGGTAC

(2) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

GATGAGTCAG GAATGCCAAA GGAACGATTT

(2) INFORMATION FOR SEQ ID NO:73:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

CAAGAAACGG AGATGCACAA GAAGCGATTC

(2) INFORMATION FOR SEQ ID NO:74:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

ACCGACAGGC TGCAGGCAGG GGCCTCCAGC

(2) INFORMATION FOR SEQ ID NO:75:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

CCCTAGCAGG ATCTCATAGA GGATGGTGGC

(2) INFORMATION FOR SEQ ID NO:76:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

CCCTAGCAAG ATCTCATAGA GGATGGTGGC

(2) INFORMATION FOR SEQ ID NO:77:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

CTCTGCTTCT GATGGCTCAA ACACAGCGAC

(2) INFORMATION FOR SEQ ID NO:78:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

CTCGGGTGGG AACACCTTGT TCAGGTCCTC

(2) INFORMATION FOR SEQ ID NO:79:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

CTCGGGTGGG AACACGTTTT TCAGGTCCTC

Claims

1. A method of treating rheumatoid arthritis in a mammal comprising:
obtaining a sample of synovium from the mammal;
identifying in said sample T cell receptor variable regions; and
administering to said mammal an effective amount of antibodies to at least one of said T cell receptor variable regions or antigenic fragments thereof.

2. The method of claim 1 wherein said mammal is a human.

3. The method of claim 1 wherein said sample of synovium is synovial tissue or synovial fluid.

4. A method of treating rheumatoid arthritis in a mammal comprising:
administering to said mammal an effective amount of antibodies to mammalian T cell receptor variable regions selected from the group consisting of Vα17, Vα1, Vβ12, Vβ14, Vβ17 and Vβ7 and antigenic fragments thereof.

5. The method of claim 4 wherein said antibody is specific for at least a portion of one or more peptides having amino acid sequences as set forth in Table 1.

6. The method of claim 4 wherein the mammal is human.

7. A method for immunizing a mammal to prevent the occurrence of rheumatoid arthritis comprising:
administering to said mammal mammalian T cell receptor variable regions selected from the group consisting of Vα17, Vα1, Vβ12, Vβ14, Vβ17, Vβ7 and antigenic fragments thereof.

8. The method of claim 7 wherein the mammal is a human and the mammalian T cell receptor variable regions are human T cell receptor variable regions.

9. The method of claim 7 wherein the mammal is a human and the mammalian T cell receptor variable regions comprise at least a portion of one of the amino acid sequences set forth in Table 1.

10. A method for immunizing a mammal to treat rheumatoid arthritis comprising:
administering to said mammal mammalian T cell receptor variable regions selected from the group consisting of Vα17, Vα1, Vβ12, Vβ14, Vβ17, Vβ7 and antigenic fragments thereof.

11. The method of claim 10 wherein the mammal is a human and the mammalian T cell receptor variable regions are human T cell receptor variable regions.

12. The method of claim 10 wherein the mammal is a human and the mammalian T cell receptor variable regions comprise at least a portion of one of the amino acid sequences set forth in Table 1.

13. A kit comprising mammalian T cell receptor variable regions selected from the group consisting of Vα17, Vα1, Vβ12, Vβ14, Vβ17 and Vβ7 and antigenic fragments thereof.

14. The kit of claim 13 wherein the mammalian T cell receptor variable regions are human T cell receptor variable regions.

15. The kit of claim 14 wherein the mammalian T cell receptor variable regions comprise at least a portion of one of the amino acid sequences set forth in Table 1.

16. A kit comprising antibodies to mammalian T cell r ceptor variable regions selected from the group consisting of Vα17, Vα1, Vβ12, Vβ14, Vβ17 and Vβ7 and antigenic fragments thereof.

17. The kit of claim 16 wherein the mammalian T cell receptor variable regions are human T cell receptor variable regions.

18. The kit of claim 17 wherein the variable regions comprise at least a portion of one of the amino acid sequences set forth in Table 1.

Fig. 1A

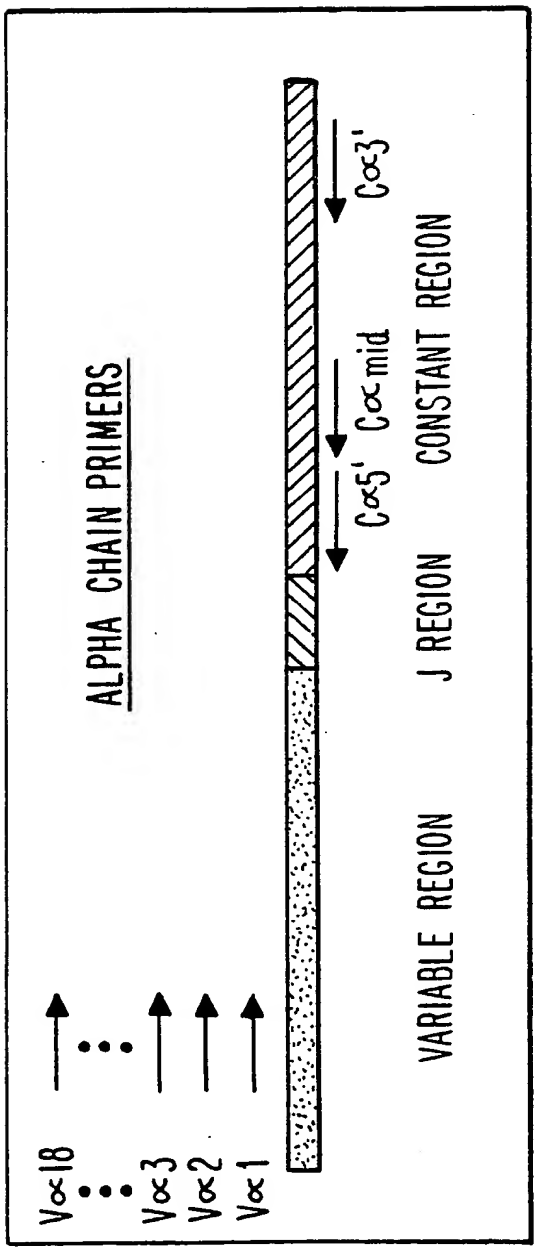

ALPHA CHAIN PRIMERS
Vα18
Vα3
Vα2
Vα1
Cα5' Cα mid
Cα3'
VARIABLE REGION
J REGION
CONSTANT REGION

Fig. 1B

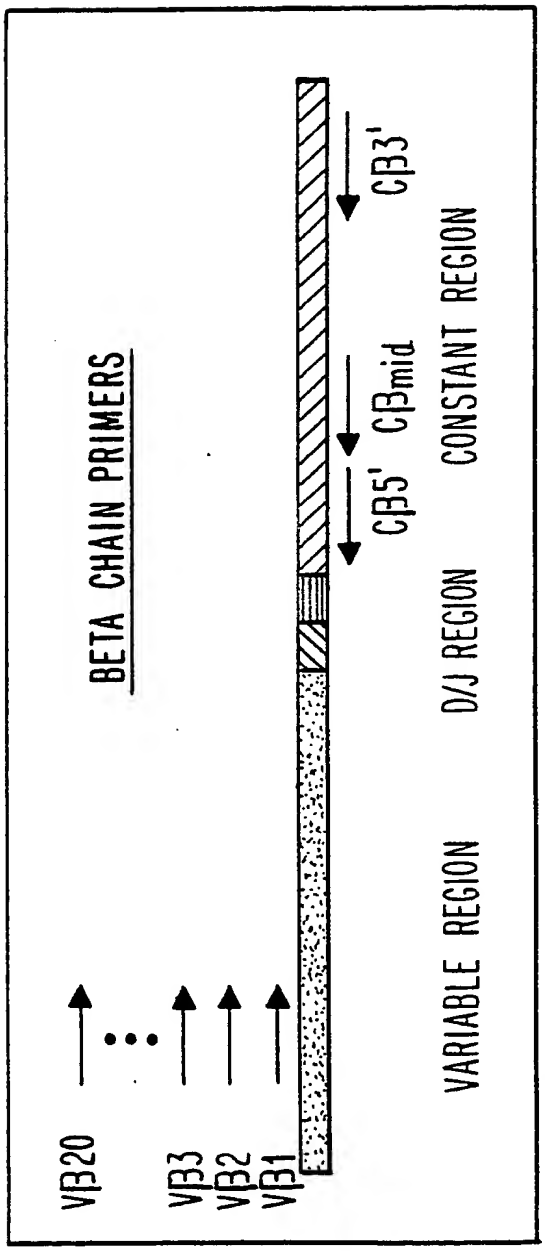

BETA CHAIN PRIMERS
VB20
VB3
VB2
VB1
CB5' CBmid
CB3'
VARIABLE REGION
D/J REGION
CONSTANT REGION

FIG. 2A

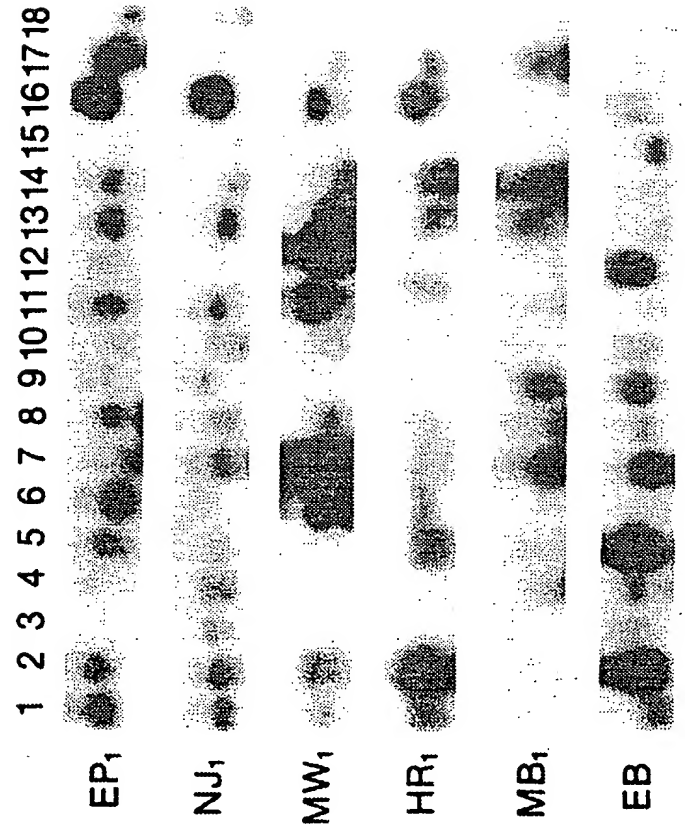
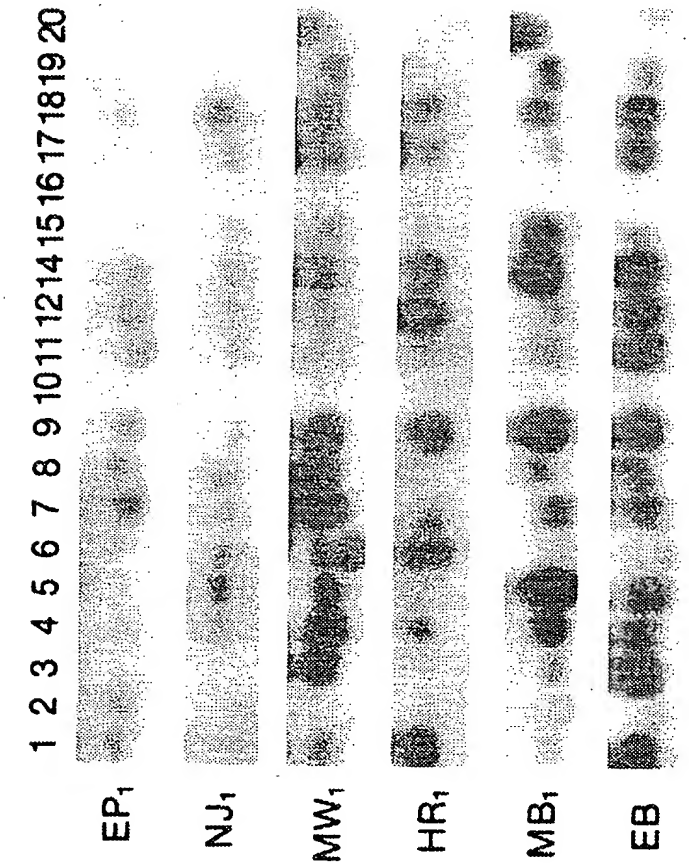

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
EP1
NJ1
MW1
HR1
MB1
EB
α

FIG. 2B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EP1
NJ1
MW1
HR1
MB1
EB
β

FIG. 3A

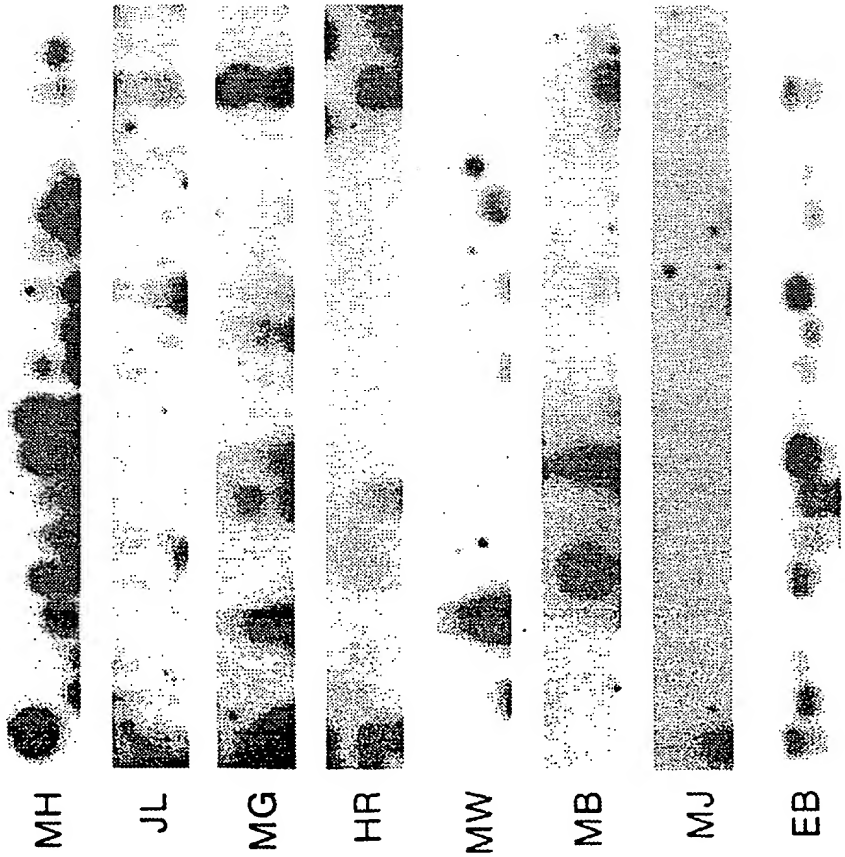
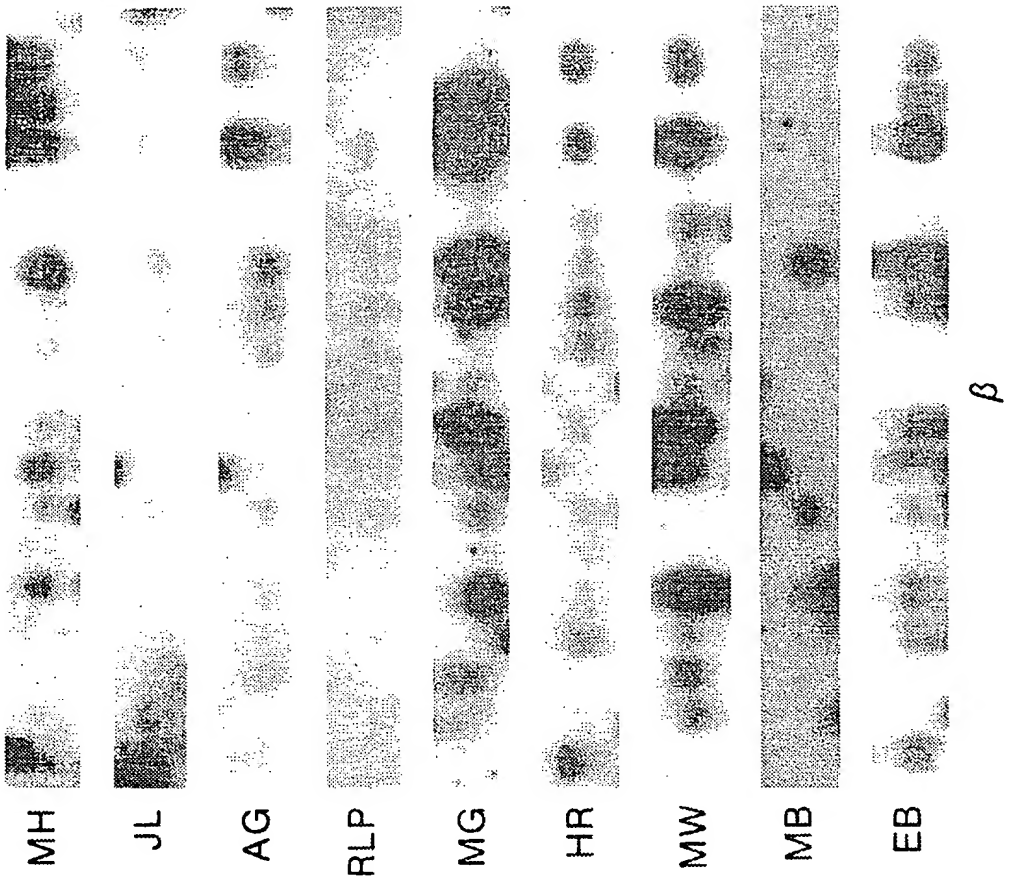

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
MH
JL
MG
HR
MW
MB
MJ
EB
α

FIG. 3B


1 2 3 4 5 6 7 8 9 10 11 12 14 15 16 17 18 19 20
MH
JL
AG
RLP
MG
HR
MW
MB
EB
β

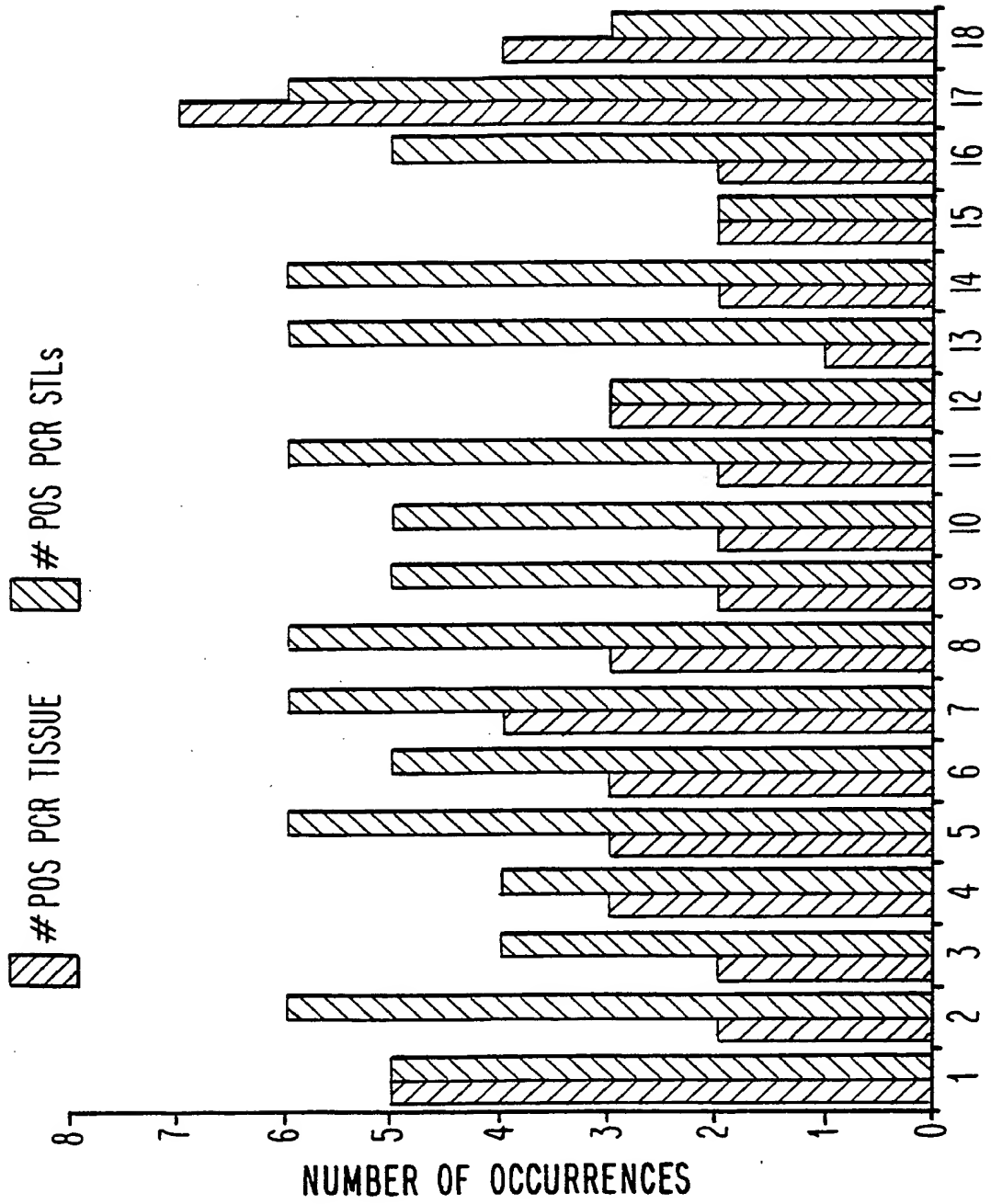

#POS PCR TISSUE
#POS PCR STLs
NUMBER OF OCCURRENCES
0
1
2
3
4
5
6
7
8
V ALPHA CHAINS
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18

Fig. 4A

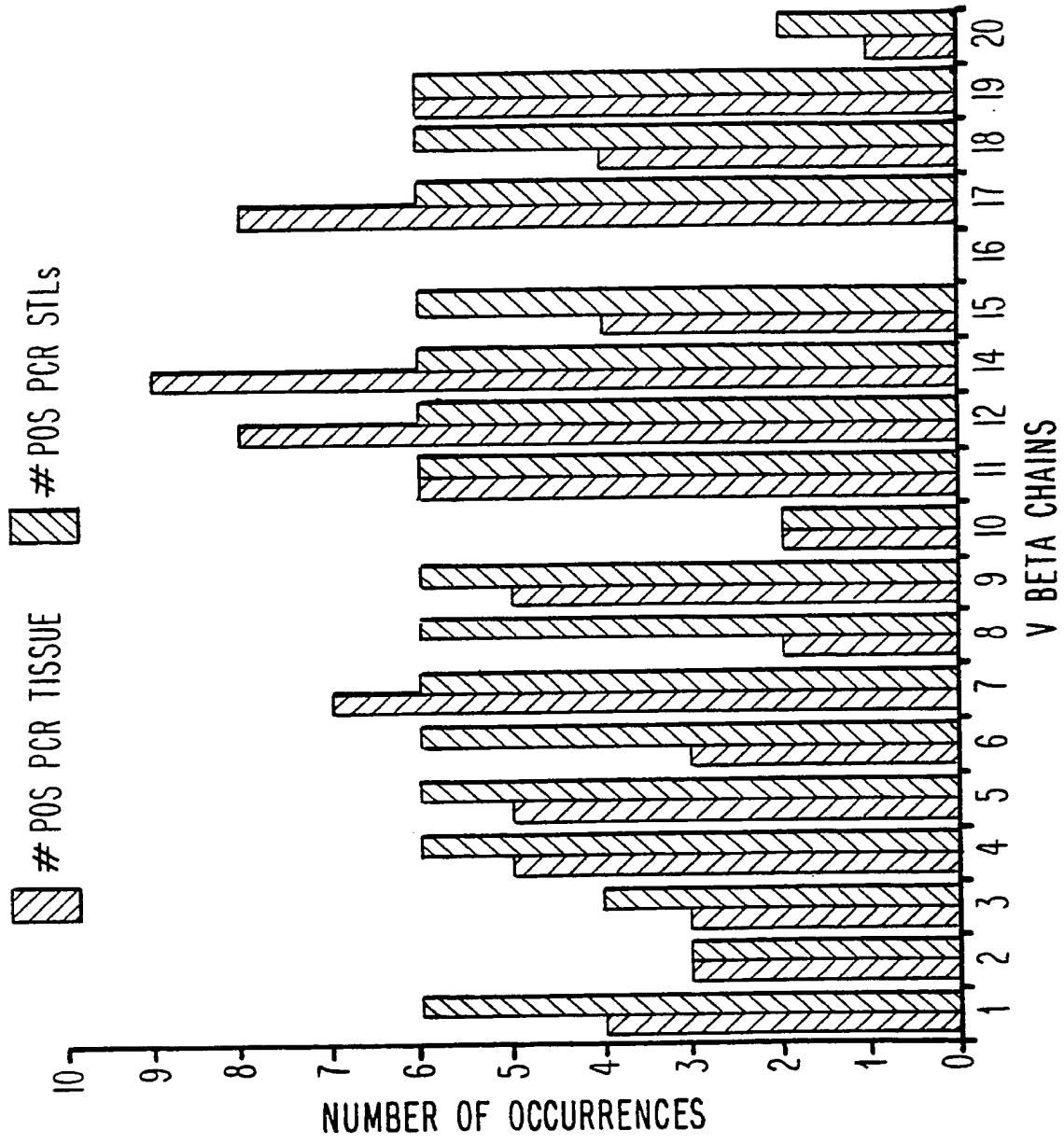

POS PCR TISSUE
POS PCR STLs
NUMBER OF OCCURRENCES
V BETA CHAINS
0 1 2 3 4 5 6 7 8 9 10
1 2 3 4 5 6 7 8 9 10 11 12 14 15 16 17 18 19 20

Fig. 4B

FIGURE 5

Vα1	CTGAGGTGCAACTACTCA
Vα2	GTGTTCCCAGAGGGAGCCATTGCC
Vα3	GGTGAACAGTCAACAGGGAGA
Vα4	ACAAGCATTACTGTACTCCTA
Vα5	GGCCCTGAACATTCAGGA
Vα6	GTCACTTTCTAGCCTGCTGA
Vα7	AGGAGCCATTGGTCCAGATAAA
Vα8	GGAGAGAATGTGGAGCAGCATC
Vα9	ATCTCAGTGCTTGTGATAATA
Vα10	ACCCAGCTGGTGGAGCAGAGCCCT
Vα11	AGAAAGCAAGGACCAAGTGTT
Vα12	CAGAAGGTAACTCAAGCGCAGACT
Vα13	GCTTATGAGAACACTGCGT
Vα14	GCAGCTTCCCTTCCAGCAAT
Vα15	AGAACCTGACTGCCCAGGAA
Vα16	CATCTCCATGGACTCATATGA
Vα17	GACTATACTAACAGCATGT
Vα18	TGTCAGGCAATGACAAGG
*Cα3'	AATAGGTCGAGACACTTGTCACTGGA
*Cαmid	CTTGTCACTGGATTTAGATCTCTCAGCTG
*Cα5'	GTACACGGCAGGGTCAGGGTTCTGGATATT
Vβ1	AAGAGAGAGCAAAAGGAAACATTCTTGAAC
Vβ2	GCTGCAAGGCCACATACGAGCAAGGCGTCG
Vβ3	AAAATGAAAGAAAAAGGAGATATTCCTGAG
Vβ4	CTGAGGCCACATATGAGAGTGGATTTGTCA
Vβ5	CAGAGAAACAAAGGAAACTTCCCTGGTCGA
Vβ6	GGGTGCGGCAGATGACTCAGGGCTGCCCAA
Vβ7	ATAAATGAAAGTGTGCCAAGTCGCTTCTCA
Vβ8	AACGTTCCGATAGATGATTCAGGGATGCCC
Vβ9	CATTATAAATGAAACAGTTCCAAATCGCTT
Vβ10	CTTATTCAGAAAGCAGAAATAATCAATGAG
Vβ11	TCCACAGAGAAGGGAGATCTTTCCTCTGAG
Vβ12	GATACTGACAAAGGAGAAGTCTCAGATGGC
Vβ14	GTGACTGATAAGGGAGATGTTCCTGAAGGG
Vβ15	GATATAAACAAAGGAGAGATCTCTGATGGA
Vβ16	CATGATAATCTTTATCGACGTGTTATGGGA
Vβ17	TTTCAGAAAGGAGATATAGCTGAAGGGTAC
Vβ18	GATGAGTCAGGAATGCCAAAGGAACGATTT
Vβ19	CAAGAAACGGAGATGCACAAGAAGCGATTC
Vβ20	ACCGACAGGCTGCAGGCAGGGGCCTCCAGC
*$C\beta_1$3'	CCCTAGCAGGATCTCATAGAGGATGGTGGC
*$C\beta_2$3'	CCCTAGCAAGATCTCATAGAGGATGGTGGC
*Cβmid	CTCTGCTTCTGATGGCTCAAACACAGCGAC
*$C\beta_1$5'	CTCGGGTGGGAACACCTTGTTCAGGTCCTC
*$C\beta_2$5'	CTCGGGTGGGAACACGTTTTTCAGGTCCTC

Pt	Vβ 1	Vβ 2	Vβ 3	Vβ 4	Vβ 5	Vβ 6	Vβ 7	Vβ 8	Vβ 9	Vβ 10	Vβ 11	Vβ 12	Vβ 14	Vβ 15	Vβ 17	Vβ 18	Vβ 19	Vβ 20	
MH	+	+		+	+	+	+	+	+		+	+	+		+	+	+		
JL	?	?					+	?			+	+	+	+	+	+	+	+	
AG	+		+		+		+	?			+	+	+		+		+		
RLP												+	+		+				
MG			+	+			+	?	+	+		+	+		+	+			
HR	+			+	+	+	+	?	+	?	+	+	+	+	+		+		
MW		+	+	+	+			?	+	+	+	+	+	+	+		+		
MB							+	?					+						
MJ								?		?									
EB	+	+		+	+	+	+	+	+		+	+	+	+	+	+	+		
# +	4	3	3	5	5	3	7	2	5	2	6	8*	9*	4	8*	4	6	1	

Fig. 6

Patient	Vα 1	Vα 2	Vα 3	Vα 4	Vα 5	Vα 6	Vα 7	Vα 8	Vα 9	Vα 10	Vα 11	Vα 12	Vα 13	Vα 14	Vα 15	Vα 16	Vα 17	Vα 18
MH	+	+	+	+	+	+	+	+	+	+		+	+	?	+		+	+
JL						?						+					+	
AG																	+	+
RLP																+		
MG	+			+			+				?						+	
HR	+						+										+	
MW				+										+				
MB						+		+									+	
MJ	+											+						
EB	+	+	+		+	+	+	+	+	+	+	+		+	+	+	+	+
#+	5	2	2	3	3	3	4	3	2	2	2	3	1	2	2	2	7*	4

Fig. 7

INTERNATIONAL SEARCH REPORT

Internauonal application No.
PCT/US92/07289

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 39/00, 39/395; C07K 7/10, 15/06, 15/28; G01N 33/53
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/324, 350,388.22, 388.75, 388.85, 389.1, 389.6; 424/85.8, 88; 435/7.24

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,886,743 (Hood et al.) 12 December 1989, Abstract and claims 54-55.	1-6, 16-18
Y	WO, A, 90/11294 (HOWELL ET AL) 04 October 1990, page 16 and claims 20-24.	1-18
Y	Eur. J. Immunol., Volume 20, issued 1990, S. Yoshino et al., " Suppression and prevention of adjuvant arthritis in rats by a monoclonal antibody to the alpha/beta T cell receptor ", pages 2805-2808, especially page 2805.	1-6, 16-18

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date f th actual completion of th international search 04 NOVEMBER 1992	Date f mailing of the internati nal search report 24 NOV 1992
Name and mailing address of the ISA/ Commissioner of Patents and Trademarks Box PCT	Authorized officer CHRISTINA CHAN

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Brit. J. Rheumatol., issued 1991, G. Kingsley, " Monoclonal antibody treatment of rheumatoid arthritis ", pages 33-35, especially page 34.	1-6, 16-18
Y	Proc. Natl. Acad. Sci. USA, Volume 85, issued November 1988, K. Sakai et al., " Involvement of distinct murine T-cell receptors in the autoimmune encephalitogenic response to nested epitopes of myelin basic protein ", pages 8608-8612, especially page 8612.	1-18
Y	Clin. Exp. Immunol., Volume 49, issued 1982, O. Duke et al., " An immunohistological analysis of lymphocyte subpopulations and their microenvironment in the synovial membranes of patients with rheumatoid arthritis using monoclonal antibodies ", pages 22-30, especially page 22.	1-18
Y	Science, Volume 253, issued 19 July 1991, X. Paliard et al., " Evidence for the effects of a superantigen in rheumatoid arthritis ", pages 325-329, especially page 325.	1-18
Y	Proc. Natl. Acad. Sci USA, Volume 86, issued November 1989, Y. Choi et al., " Interaction of Staphylococcus aureus toxin " superantigens " with human T cells ", pages 8941-8945, especially page 8945.	1-18
Y	Nature, Volume 341, issued 12 October 1989, A. Vandenbark et al., " Immunization with a synthetic T-cell receptor V-region peptide protects against experimental autoimmune encephalomyelitis ", pages 541-544, especially page 541.	7-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/07289

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

I. Claims 1-6 and 16-18, drawn to a method and a kit involving antibodies, classified in Class 424 Subclass 85.8.

II. Claims 7-15, drawn to a method and a kit involving T cell receptor variable regions, classified in Class 424 Subclass 88.

The inventions as grouped are distinct, each from the other, because they represent different inventive endeavors. The method and the kit in Group I would not suggest the method and the kit in Group II. They are unrelated in operation and one does not require the other for ultimate use and the specification does not disclose a dependent relationship among them.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims. (Telephone Practice)

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any addtional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention frist mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL [redacted]RCH REPORT

[redacted]ternational application No.
[redacted]T/US92/07289

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

530/324, 350,388.22, 388.75, 388.85, 389.1, 389.6; 424/85.8, 88; 435/7.24